

Entry Level Clinical Nutrition Part XII

Micronutrient imbalances:
Water soluble vitamins

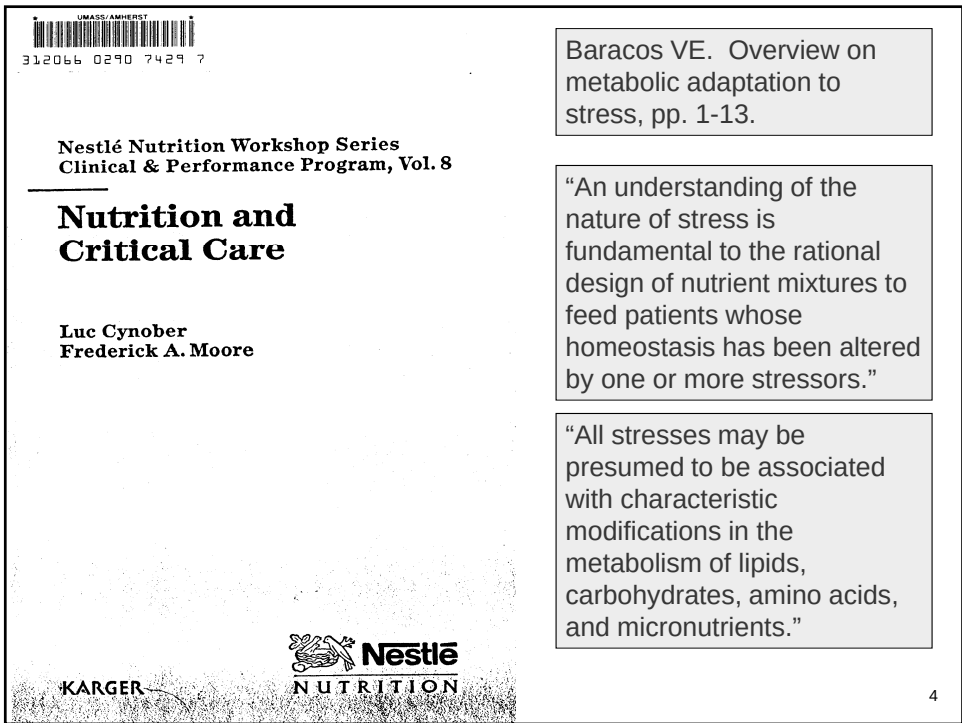
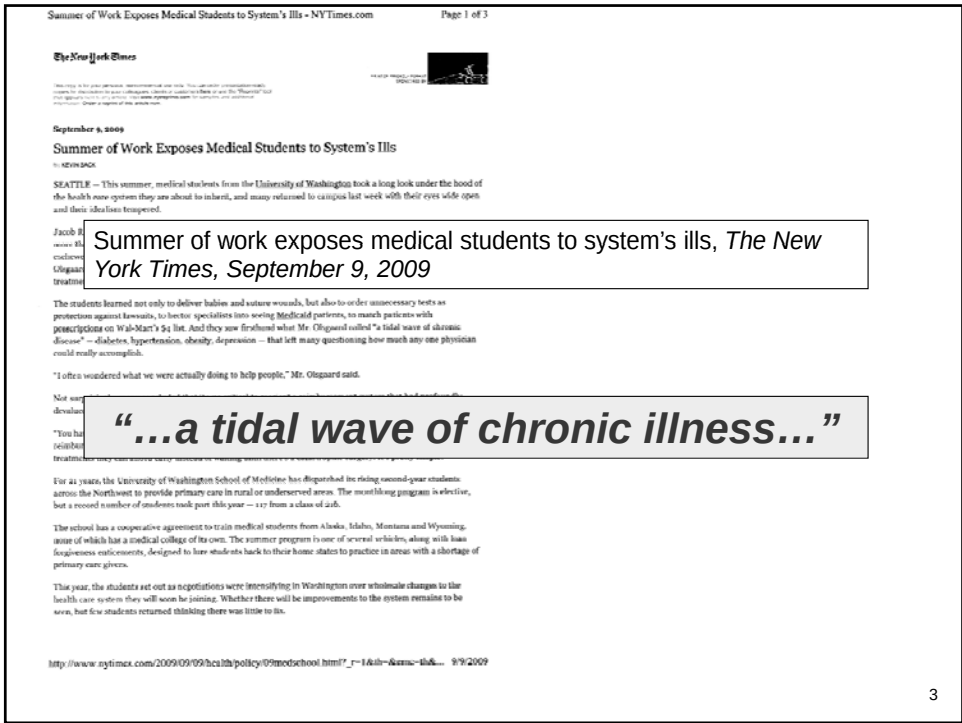
Jeffrey Moss, DDS, CNS, DACBN
jeffmoss@mossnutrition.com
413-530-0858 (cell)

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

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Entry Level Clinical Nutrition – Part 12
Dr. Jeff Moss



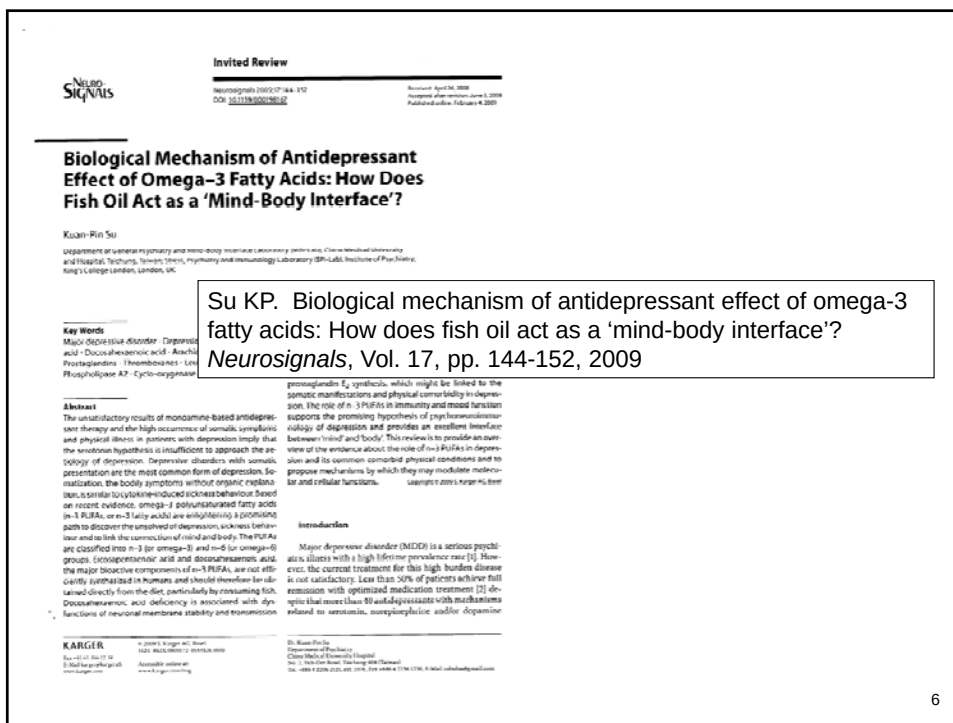
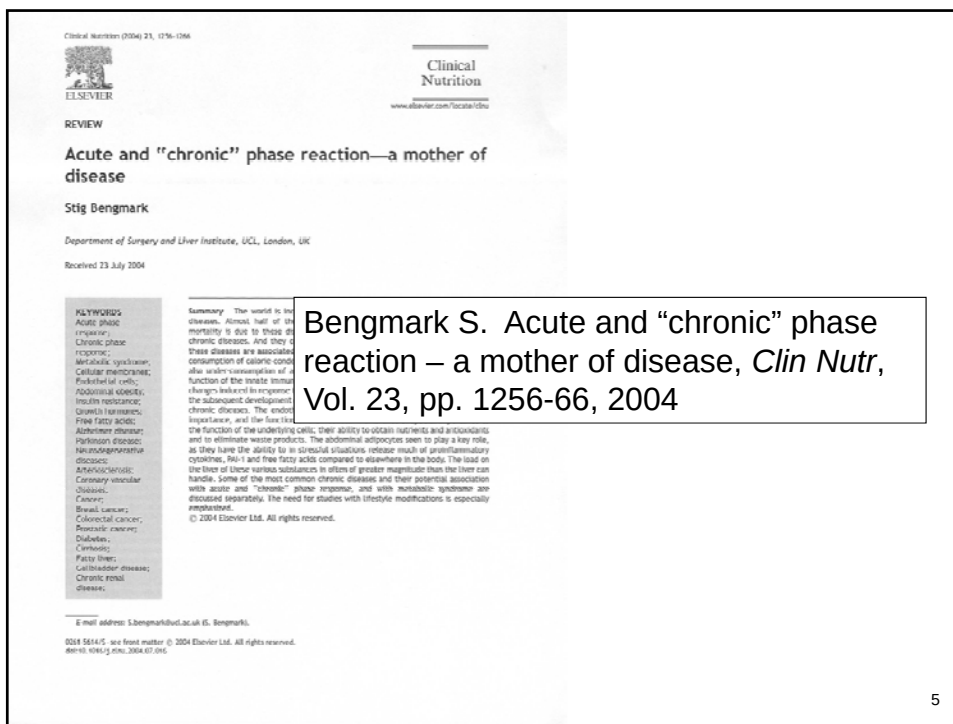


Table 1. Overlapping of symptoms of acute sickness behaviour associated with IFN- α therapy and the somatic symptoms in MDD

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 ^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.

- ## 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

Underlying hypotheses of Entry Level Clinical Nutrition:

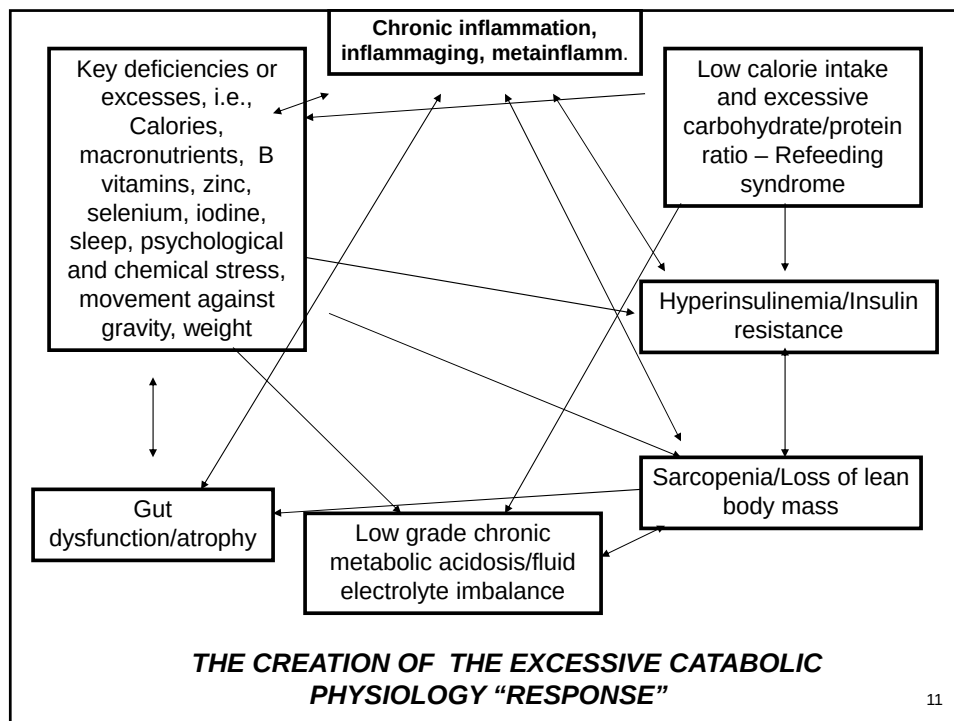
- Chief complaints in chronically ill patients are not diseases but responses that have gone on too long (Allostatic load).
- The metabolic imbalances that combine to form this response have been well defined by critical care nutritionists.

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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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Foundational hypothesis

- Issues relating to micronutrient status in chronically ill patients are more than just issues of dietary adequacy and bioavailability.
- How nutrients are metabolized after absorption may be just as important to resolving chief complaints in chronically ill patients, if not more so.

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Foundational hypotheses

- What is the major driver of aberrant micronutrient metabolism in chronically ill patients?

INFLAMMATION!!

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Clinical Nutrition (2006) 25, 1-13

Clinical Nutrition

http://journals.elsevier.com/clinicalnutrition

REVIEW

The key role of micronutrients[☆]

Alan Shenkin^{*}

Division of Clinical Chemistry, F&M
Received 9 November 2005; accepted 10 November 2005

Abstract

Micronutrient deficiency can lead to disease, but effects in preventing or treating disease which is not due to micronutrient deficiency cannot be expected from increasing the intake. There is a highly integrated system to control the flux of micronutrients in illness, and this demonstrates, just how important the body performs the micronutrients to do. An adequate intake therefore is necessary to sustain metabolism and tissue function, but provision of excess supplements to individuals who do not need them may be harmful. Clinical benefit is most likely in those individuals who are severely depleted and at risk

KEYWORDS:
Trace elements;
vitamins;
antioxidants;
SOD;
Taq;
severe;
vitamins.

“Micronutrients play a central role in metabolism and in the maintenance of tissue function, but effects in preventing or treating disease which is not due to micronutrient deficiency cannot be expected from increasing the intake.”

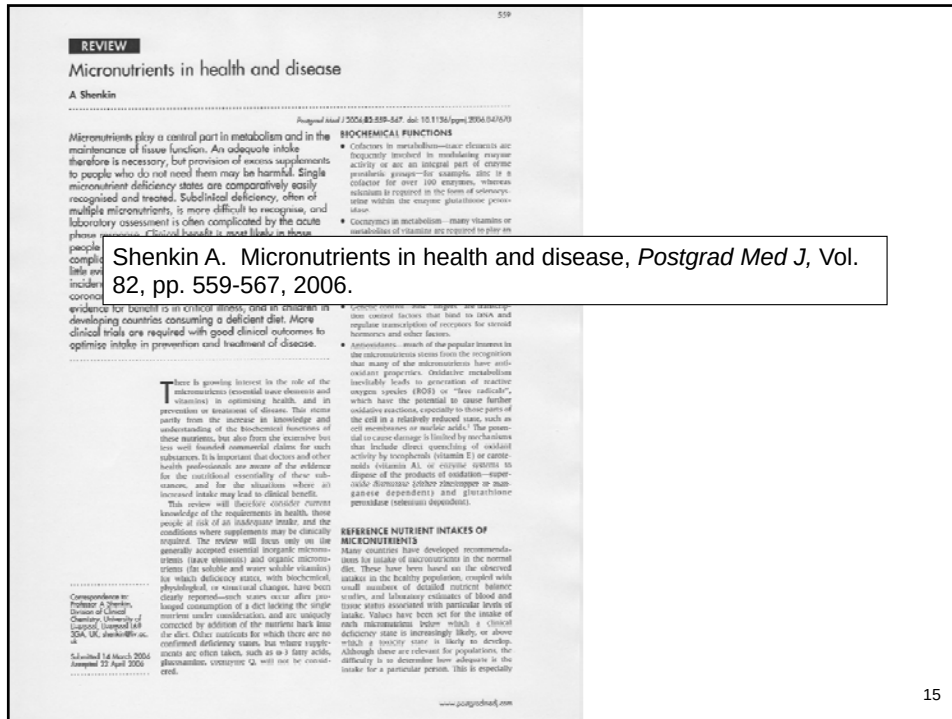
Shenkin A. The key role of micronutrients, *Clin Nutr*, Vol. 25, pp. 1-13, 2006

“There is a highly integrated system to control the flux of micronutrients in illness...”

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- “The catabolism associated with acute infection, surgery, or trauma leads to increased energy expenditure and net protein breakdown.”
- “Requirements for water soluble vitamins, as coenzymes for these metabolic pathways, will be increased, as will the requirements for various trace elements.”

- “Anabolism increases the requirement for all nutrients; hence increased micronutrients should be supplied when patients are gaining weight.”
- “Trace element deficiencies are more likely when patients become anabolic, after a prolonged period of catabolism.”

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Review Article *Ann Clin Biochem* 2000; 37: 289-297

Effect of the inflammatory response on trace element and vitamin status

Peter Galloway¹, Donald C McMillan² and Naveed Sattar¹

From the Departments of ¹Psychological Biochemistry and ²Surgery, Royal Infirmary University NHS Trust, Glasgow G41 1JX, UK

Trace elements and vitamins are required in milligram amounts per day to sustain normal health. If insufficient or excessive amounts are present, illness can result. Improvements in atomic absorption spectroscopy for trace metals in the 1970s and high performance chromatography methods for vitamins in the 1990s now allow us to detect physiological and pathological variations in blood concentrations of these substances in the absence of clinical evidence of deficiency or toxicity.

Several epidemiological studies highlighted the association of a circulating concentration of micronutrients and trace elements with an increased risk of cardiovascular disease and cancer. It is proposed to reduce this risk by depleting concentrations of these by increased intake. However, it is more appropriate to supplement with micronutrients if deficiency is present. It is emphasized that the relationship between serum concentrations and clinical risk is more complex than this and would suggest.

Inflammation is also increasingly recognized as playing an important role in the pathogenesis of cardiovascular disease and of cancer.^{1,2} In cardiovascular disease, there is a strong relationship between circulating C-reactive protein (CRP) concentrations and future myocardial events and infarction.³ Similarly, in cancer it has been known for some time that disease progression and lower survival in patients with elevated serum is associated with higher CRP concentrations.⁴⁻⁶ Indeed,

when promising markers of the progression of cardiovascular and gastrointestinal cancer (e.g. plasminogen activator inhibitor 1) can be related to the presence of an inflammatory response (i.e. CRP) and its magnitude.^{7,8}

The inflammatory response is a coordinated sequence of reactions involving biochemical and physiological changes whose aim is to limit damage and aid repair.⁹ In the short term these changes are primarily aimed at neutralizing the offending agent.

Galloway P et al. Effect of the inflammatory response on trace element and vitamin status, *Ann Clin Biochem*, Vol. 37, pp. 289-297, 2000.

protein transferrin, albumin and ceruloplasmin, and those of selenium and commonly measured vitamins, in various clinical settings. We discuss the significance of such changes in the monitoring of nutritional status in acutely and chronically ill patients.

TRACE METALS

Iron

It is well established that iron is a negative acute-phase reactant, serum iron concentrations decrease in a wide variety of stressful situations such as surgery, major trauma, infections or neurological events.¹⁰ The fall in serum iron concentration is pronounced, commonly around 20-25%. Even greater decreases (> 50%) have been noted when two stressful events occur simultaneously.¹¹ The reduction in iron concentration is also marked (around 40%) after major trauma such as regional hepatic injury, when CRP concentration increases to approximately

This article was prepared for the inclusion of the Clinical Laboratory Investigation Working Committee of the Association of Clinical Biochemists.
Correspondence: Dr Peter Galloway, Clinical Pathology Laboratory, Department of Pathology, Royal Infirmary, 4th Floor Q15, Royal Infirmary NHS Trust, Glasgow G41 1JX, UK.
Tel: +44(0)141 275 1212 Fax: +44(0)141 275 1258.
E-mail: peter.galloway@nhs.uk

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TABLE 1. Relationship of the inflammatory response and circulating micronutrient concentrations

Analytes	Reference range	Minor inflammation (CRP< 15 mg/L)	Major inflammation (CRP~ 100-200 mg/L)	Comments
Iron	8-30 µmol/L	Decreased by 40%	Decreased by 60-90%	Liver uptake
Zinc	12-18 µmol/L	Decreased by 10%	Decreased by 40-60%	Liver uptake
Selenium	0.8-2.0 µmol/L	Decreased by 10%	Decreased by 40-60%	? Redistribution
Copper	11.5-23.5 µmol/L	Increased by 10-15%	Increased by 30%	? Liver extraction
Vitamin A	1.0-2.8 µmol/L	Decreased by 30-40%	Decreased by 30%	Probable redistribution
Vitamin E	15-40 µmol/L	Negligible	Decreased by 20-30%	More data needed
Vitamin C	10-115 µmol/L	No data	Minimal to > 75% dec.	More data needed
Vitamin B ₁	280-540 ng TDP/gHb	No data	No change	More data needed
Vitamin B ₂	< 70% activation*	No data	No change	More data needed
Vitamin B ₆	18-135 nmol/L (PP)	No data	Decreased by 40-50%	More data needed
Vitamin B ₁₂	188-1059 pg/mL	No data	No change	More data needed
Folate	3.5-16.0 ng/mL	No data	No change	More data needed
Lycopene	100-300 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
β-carotene	92-312 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
α-carotene	14-60 µg/L	Decreased by ~50%	Decreased by > 90%	More data needed
Lutein	82-202 µg/L	Minimal change	Decreased by ~70%	More data needed

An approximate guide to the extent of change seen in analytes with different degrees of inflammation. The figures quoted are collated from disparate sources and the effects of diverse factors in different pathophysiologies may be important. TDP=thiamine diphosphate; *=of red cell glutathione reductase; PP=pyridoxal phosphate.

Ann Clin Biochem 2000; 37

A notable exception:
Refeeding syndrome and
vitamin B1 (Thiamine)

What is refeeding syndrome?

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Wiley Publishing Corporation
Gastroenterology Research and Practice
Volume 2011 | Article ID 410971 | 4 pages
doi:10.1155/2011/410971

Review Article Refeeding Syndrome: A Literature Review

L. U. R. Khan, I. Ahmed, S. Khan, and J. MacFie

The Combined Gastroenterology Research Unit, Scarborough Hospital, Woodland Drive, Scarborough YO11 4QF, UK

Correspondence should be addressed to I. Ahmed, drjeff@hotmail.co.uk

Received 1 June 2010; Revised 21 July 2010; Accepted 5 August 2010

Academic Editor: Remy Meier

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Refeeding syndrome (RFS) describes the biochemical changes, clinical manifestations, and complications that can occur as a

Khan IUR et al. Refeeding syndrome: A literature review,
Gastroenterology Res Pract, Vol. 2011, Article ID: 410971, 2010.

1. Introduction

RFS is well recognized. It occurs after the reintroduction of feeding after a period of starvation or fasting [1]. RFS describes a series of metabolic and biochemical changes that occur as a consequence of reintroduction of feeding after a period of starvation or fasting. This unfavorable metabolic response causes nonimmune-mediated harm to the body and can be mild, moderate, or severe. Although the physiology and pathophysiology are well known, the circumstances under which RFS occurs, the clinical manifestations, and the management of these patients are less clear [2, 3].

1.1. Methods: A PubMed search for the terms "refeeding syndrome" AND "hypophosphatemia" generated two hundred and seven separate articles. There were no randomized controlled trials identified.

1.2. Physiology: With food in abundance, carbohydrates provide for most of our energy requirements. Glucose, the principal product of carbohydrate digestion, is actively cotransported along with sodium at the intestinal brush border against a concentration gradient. Glucose enters the portal circulation by facilitated diffusion and blood sugar levels rise. This stimulates the release of the peptide hormone insulin from pancreatic β cells. Insulin secretion

has several effects. It promotes glucose uptake and storage (glycogenesis), inhibits the breakdown of fats (lipolysis), and increases cellular uptake of potassium. When glycogen storage capacity is exceeded, lipogenesis occurs with nonoxidized glucose being converted to fat and stored as triglycerides in adipose tissue. Together, the consequence is for blood glucose levels to fall with a concomitant reduction in insulin secretion [4].

With starvation, levels of glucose begin to fall within 14 to 72 hours. This results in the release of the peptide hormone glucagon and a reduction in insulin secretion [10]. Glucose levels are maintained by glycogenolysis but glycogen stores rarely last more than 72 hours [11]. Glucose homeostasis is essential because certain tissues, such as brain, erythrocytes, and cells of the renal medulla are obligate glucose users [12]. These demands for glucose are met by the process of gluconeogenesis by which noncarbohydrate sources are metabolized to glucose. The most important of these is the muscle protein alanine. In addition, fatty acid oxidation in liver hepatocytes generates ketone bodies. These are converted to acetyl-coenzyme-A generating energy via the Krebs cycle. Further energy production from lactate and pyruvate (the products of glycolysis) and amino acids occurs via the Cori cycle [4]. In summary, metabolic adaptations occur to ensure survival on fat fast economy [13]. There is a resultant loss of body fat and protein and an accompanying depletion of potassium, phosphate, and magnesium [14, 15].

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- **“RFS describes a series of metabolic and biochemical changes that occur as a consequence of reintroduction of feeding after a period of starvation or fasting. This unfavorable metabolic response causes nonimmune-mediated harm to the body and can be mild moderate, or severe.”**

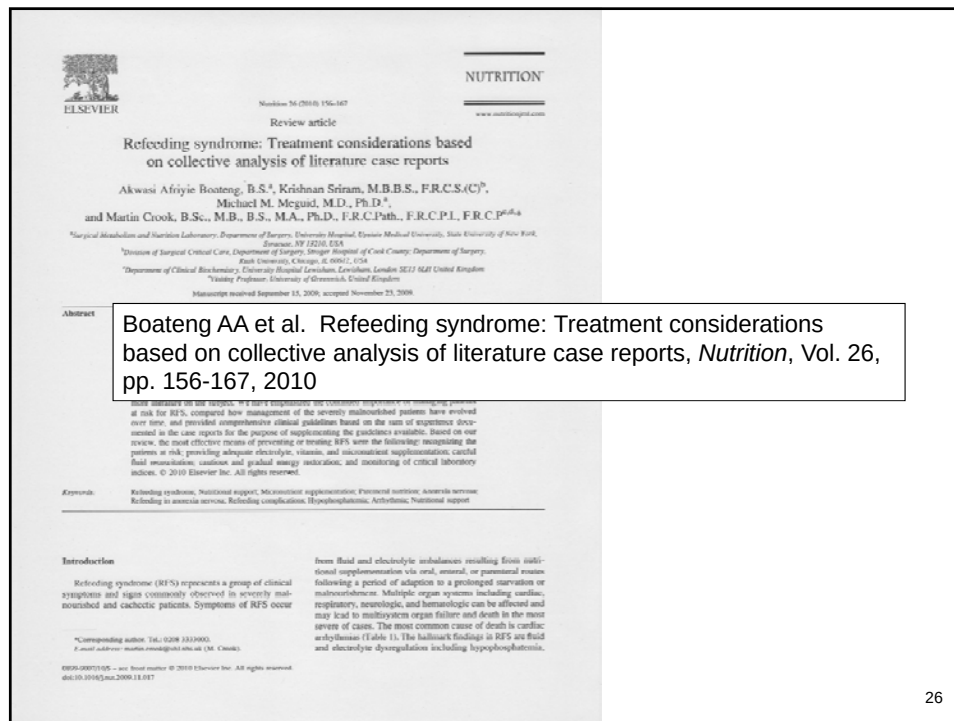
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- **“The reintroduction of nutrition to a starved or fasted individual results in a rapid decline in both gluconeogenesis and anaerobic metabolisms. This is mediated by the rapid increase in serum insulin that occurs on refeeding. Insulin stimulates the movement of extracellular potassium, phosphate, and magnesium to the intracellular compartment. Depleted intracellular stores and a large concentration gradient ensure a rapid fall in the extracellular concentration of these ions.”**

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- **“Osmotic neutrality must be maintained resulting in the retention of sodium and water. Reactivation of carbohydrate-dependent metabolic pathways increases demand for thiamine, a cofactor required for cellular enzymatic reactions. The deficiencies of phosphate, magnesium, potassium, and thiamine occur to varying degrees and have different effects in different patients.”**

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- **“The hallmark findings in refeeding syndrome (RFS) are fluid and electrolyte dysregulation including hypophosphatemia, hypokalemia, hypomagnesemia, abnormalities in glucose metabolism, vitamin (importantly thiamine), and trace element deficiencies. RFS can be viewed as spectrum disorder where symptoms range from mild to severe depending on the degree of starvation or malnourishment and the form of management employed.”**

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Thiamine

- ***“Vitamin deficiency results from the rapid depletion of vitamins after onset of refeeding due to their role in various biochemical functions. For example, thiamine is necessary for glucose metabolism but its stores are depleted during starvation. Sudden introduction of glucose drives already depleted thiamine stores to a nadir, precipitating Wernicke’s encephalopathy and lactic acidosis.”***

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Thiamine

- **“Vitamin B1 (thiamine) is not stored in sufficient amounts and, since it is needed for glycolysis, it must be provided before or along with glucose administration.”**
- **“Deficiency in thiamine also causes a buildup of pyruvic and lactic acids...”**

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European Journal of Clinical Nutrition (2008) 62, 687–694
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www.nature.com/ejcn

REVIEW

Nutrition in clinical practice—the refeeding syndrome: illustrative cases and guidelines for prevention and treatment

Z Stanga^{1,2}, A Brunner^{1,3}, M Leuenberger⁴, RF Grimble⁵, A Shenkin⁶, SP Allison⁷ and DN Lobo²

¹Department of Internal Medicine, University Hospital, Bern, Switzerland; ²Clinical Nutrition Team, Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital, Bern, Switzerland; ³Institute of Human Nutrition, Faculty of Medicine, Health and Life Sciences, University of Southampton, Southampton, UK; ⁴Institute of Clinical Chemistry, Faculty of Medicine, University of Liverpool, Liverpool, UK; ⁵Department of Clinical Nutrition, University of Liverpool, Liverpool, UK; ⁶Department of Clinical Nutrition, University of Liverpool, Liverpool, UK; ⁷Department of Clinical Nutrition, University of Liverpool, Liverpool, UK

The refeeding syndrome (RS) is a potentially fatal complication of the refeeding of malnourished individuals. The specific components of the syndrome, their physiological mechanisms, and the clinical features of the syndrome are discussed. Each case described here or more of the features of the refeeding syndrome including dehydration and low plasma levels of potassium, phosphate, magnesium and thiamine combined with salt and water retention. These refeeding syndrome cases are described with a protocol to anticipate, prevent and treat the condition in adults. (European Journal of Clinical Nutrition (2008) 62, 687–694, doi:10.1038/ejcn.2008.254; published online 15 August 2008)

Keywords: refeeding syndrome; hypophosphatemia; hypomagnesaemia; thiamine deficiency; nutritional therapy; guidelines

Intro
The refeeding syndrome (RS) is a potentially fatal complication of the refeeding of malnourished individuals. The specific components of the syndrome, their physiological mechanisms, and the clinical features of the syndrome are discussed. Each case described here or more of the features of the refeeding syndrome including dehydration and low plasma levels of potassium, phosphate, magnesium and thiamine combined with salt and water retention. These refeeding syndrome cases are described with a protocol to anticipate, prevent and treat the condition in adults. (European Journal of Clinical Nutrition (2008) 62, 687–694, doi:10.1038/ejcn.2008.254; published online 15 August 2008)

“The refeeding syndrome was first reported among those released from concentration camps following the Second World War. Oral feeding of these grossly malnourished individuals often resulted in fatal diarrhoea, heart failure and neurological complications, including coma and convulsions.”

• salt and water retention leading to oedema and heart failure, which may be exacerbated by sodium, steroids.

Received 14 February 2008; revised 17 June 2008; accepted 21 June 2008; published online 15 August 2008

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Key metabolic features

- “salt and water retention leading to oedema and heart failure, which may be exacerbated by cardiac atrophy,
- hypokalemia due to rapid cellular uptake of potassium as glucose and amino acids are taken up during cellular synthesis of glycogen and protein,
- hypophosphataemia due to increased phosphorylation of glucose,
- rapid depletion of thiamine, a cofactor in glycolysis, leading to Wernicke's encephalopathy and/or cardiomyopathy, and
- Hypomagnesaemia due to cellular uptake of this mineral.”

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Clinical presentation “in the trenches”

- “It is difficult to give a precise definition for the refeeding syndrome, since many otherwise well nourished patients, refed after only a few days starvation, will show a modest change in biochemical values, for example a fall in serum potassium and phosphate concentrations, without displaying any symptoms.”

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Clinical presentation “in the trenches”

- “There is a spectrum or gradation in the features of this condition from such asymptomatic cases to those with severe malnutrition who are at risk of overt and even life-threatening symptoms.”
- “We have taken the view that the full-blown syndrome should be defined by the presence of symptoms, but that biochemical changes of sufficient degree to pose a potential risk should be acted upon without delay in order to prevent the clinical features developing.”
- “Perhaps, we should adopt the terms ‘symptomatic refeeding syndrome’ and ‘potential or biochemical refeeding syndrome.’”

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Table 1 Some groups of malnourished patients at particular risk of developing the refeeding syndrome

Unintentional weight loss

- Loss of > 5% of body weight in 1 month
- Loss of > 7.5% of body weight in 3 months
- Loss of > 10% of body weight in 6 months

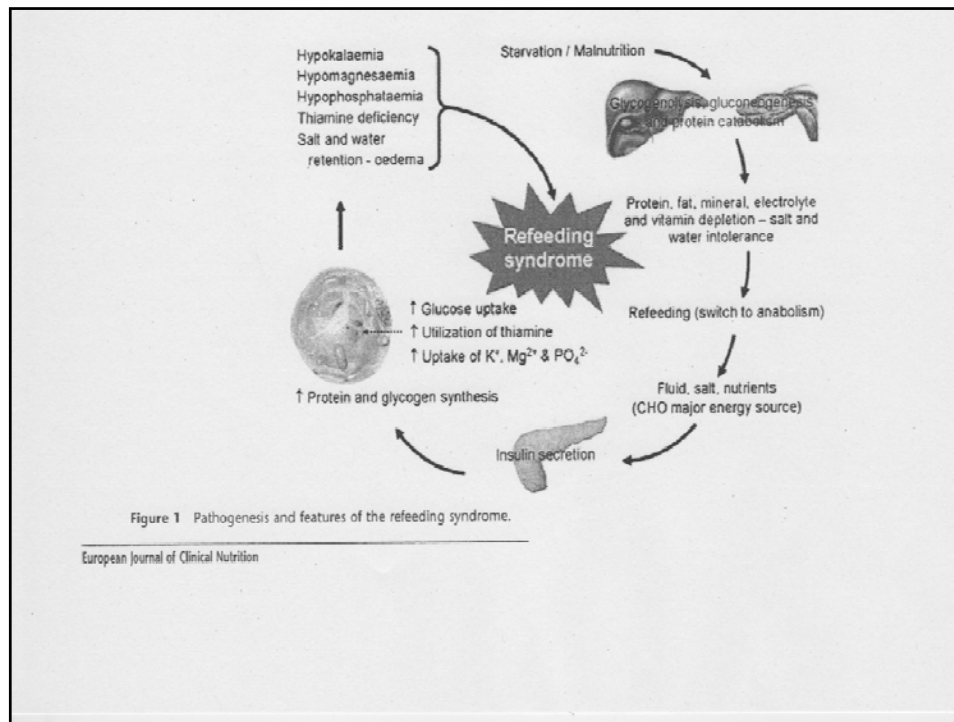
Low nutrient intake

- Patients starved for > 7 days
- Prolonged hypocaloric feeding or fasting
- Chronic swallowing problems and other neurological disorders
- Anorexia nervosa
- Chronic alcoholism
- Depression in the elderly
- Patients with cancer
- Chronic infectious diseases (AIDS, tuberculosis)
- During convalescence from catabolic illness
- Postoperative patients
- Diabetic hyperosmolar states
- Morbid obesity with profound weight loss
- Homelessness, social deprivation
- Idiosyncratic/eccentric diets
- Hunger strikers

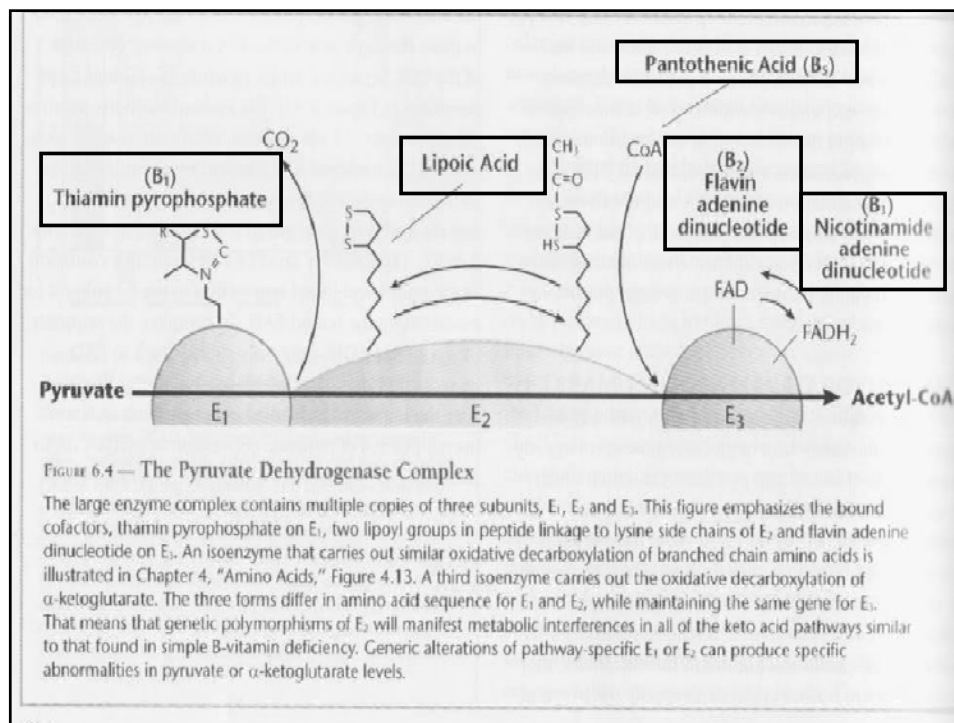
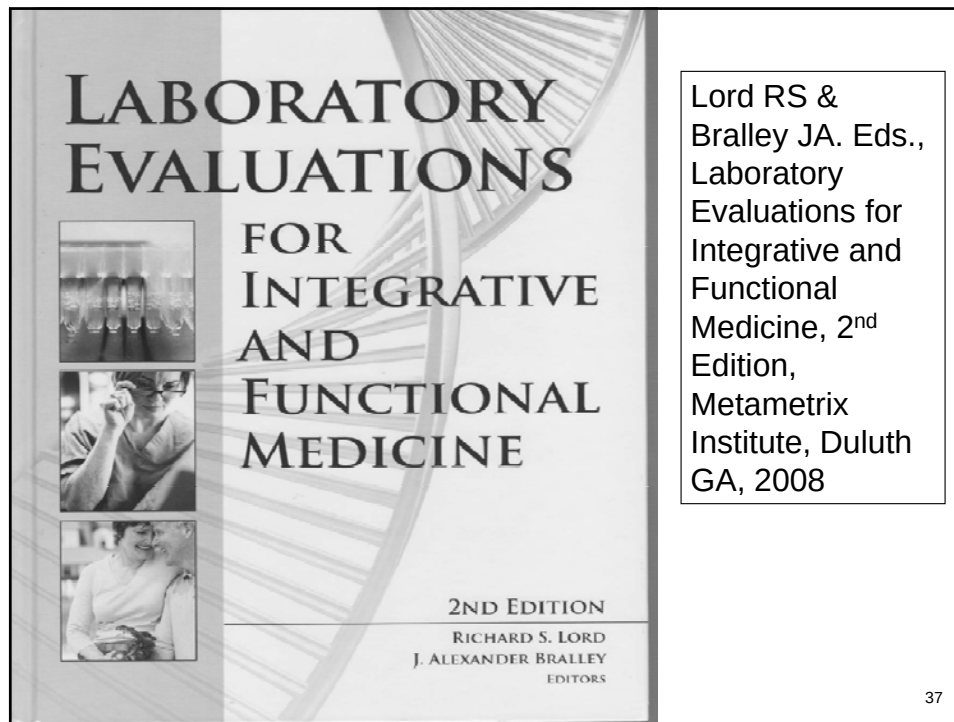
Increased nutrient losses/decreased nutrient absorption

- Significant vomiting and/or diarrhoea
- Dysfunction or inflammation of the gastrointestinal tract
- Chronic pancreatitis
- Chronic antacid users (these bind minerals)
- Chronic high-dose diuretic users
- After bariatric surgery

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B vitamins and the pyruvate dehydrogenase complex



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ADVANCES IN
ENZYME
REGULATION

Advan. Enzyme Regul. 42 (2002) 249–259

www.elsevier.com/locate/yntreg

Regulation of the activity of the pyruvate dehydrogenase complex

Robert A. Harris*, Melissa M. Bowker Kinley, Boli Huang, Pengfei Wu

Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, 635 Barnhill Drive, Indianapolis, IN 46202-5122, USA

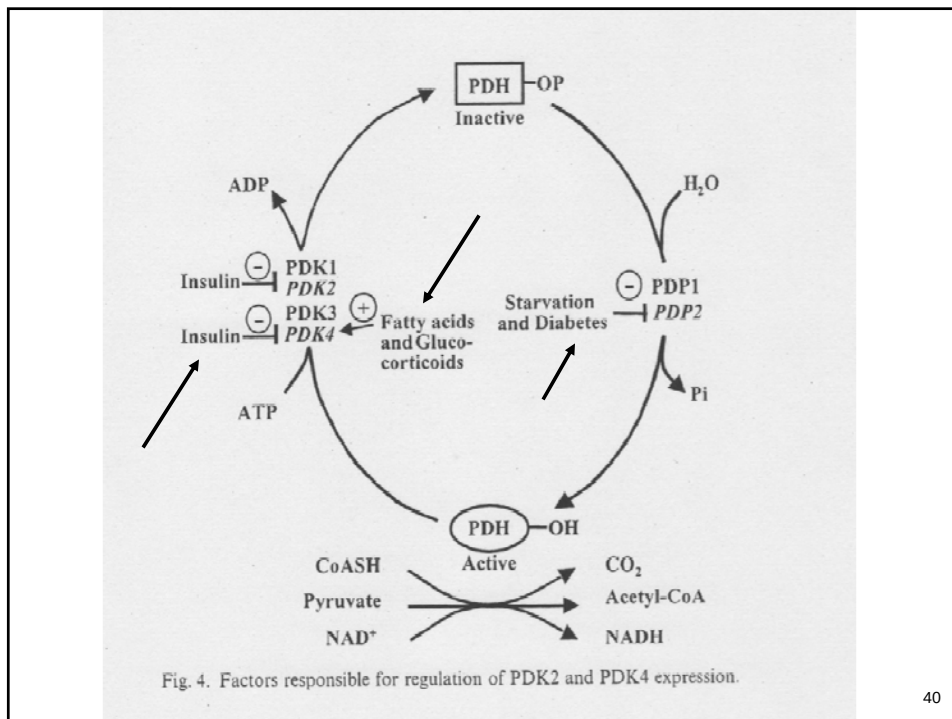
Introduction

Harris RA et al. Regulation of the activity of the pyruvate dehydrogenase complex, *Advan Enzyme Regul*, Vol. 42, pp. 249-259, 2002

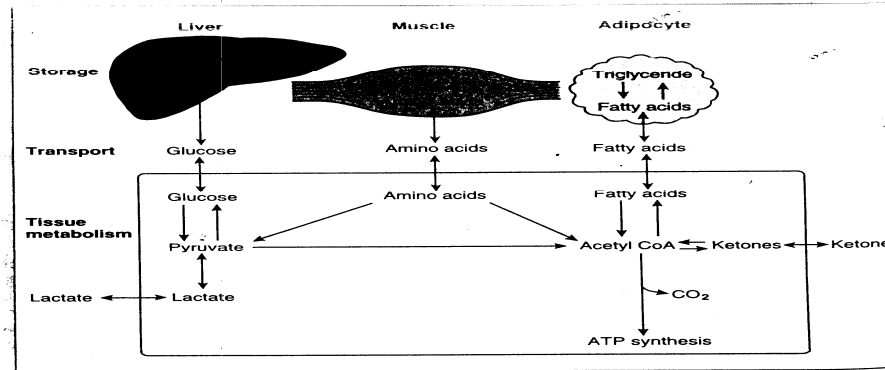
“Prolonged fasting or meals rich in fat bring about inhibition and inactivation of the pyruvate dehydrogenase complex in order to minimize loss of pyruvate carbon.”

*Corresponding author.
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PII: S0045-2718(01)00061-9

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Interconversion of Metabolic Fuels



Interconversion of metabolic fuels, Coffee CJ. Metabolism, Fence Creek Publ., Madison, CT, 1998, p. 102

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Fructose induced lipogenesis: from sugar to fat to insulin resistance

Varman T. Samuel^{1,2}

¹ Department of Internal Medicine, Yale University School of Medicine, New Haven, CT 06510-8033, USA
² Physician's Office Medical Center, West Haven, CT 06516, USA

Increasing consumption of sugars is one of the contributing factors to the obesity epidemic. Both cane sugar and high-fructose corn syrup contain glucose and fructose. Fructose, in contrast to glucose, is known to potently stimulate lipogenesis, but the mechanisms responsible are not yet fully known. This paper reviews several possible pathways that might be involved, such as activation of pyruvate carboxylase, increased activity of acetyl-CoA carboxylase, and increased activity of fatty acid synthase.

of ~18 kg per capita, the contribution to the obesity epidemic becomes more apparent. Although these numbers are useful for discussing our collective behavior, fructose consumption is not uniform across the population; consumption varies greatly between the lowest and highest consumers, the latter exemplified by adolescent males, who consume the greatest amount of fructose (estimated between 3.5-5.5 g/kg body weight per day) [1].

Samuel VT. Fructose induced lipogenesis: from sugar to fat to insulin resistance, *Trends Endocrinol Metab*, Vol. 22, No. 2, pp. 60-65, February, 2011.

Too much of anything is good for nothing. Perhaps we should have heeded the adage against that apple in the Garden of Eden, or what if the tale of Persephone and the pomegranate? It is unlikely that these tales intended to portend the perils of the fructose contained in those sweetened fruits, though now the very real dangers of fructose over-consumption are increasingly appreciated. In 2004, Bray et al. made the observation that the rising prevalence of obesity was temporally associated with the increased consumption of high-fructose corn syrup (HFCS) [2].

Within the hepatocyte, fructose is largely transported via GLUT5 and rapidly phosphorylated by fructokinase, yielding fructose 1-phosphate (Fru-1P) (Figure 1). Unlike phosphoenolpyruvate (PEP), fructokinase is not inhibited by ATP [3], and thus might not be as responsive to the cellular energy status. Thus, fructolysis lacks the tight regulation present in glycolysis. Fru-1P is subsequently cleaved by aldolase B to yield dihydroxyacetone phosphate (DHAP) and glyceraldehyde 3-phosphate (Gly-3P), whereas glyceraldehyde-3-phosphate can proceed further down the glycolytic pathway into acetyl-coenzyme A (CoA), which is either

"Fructose promotes lipogenesis by...increasing PDH activity..."

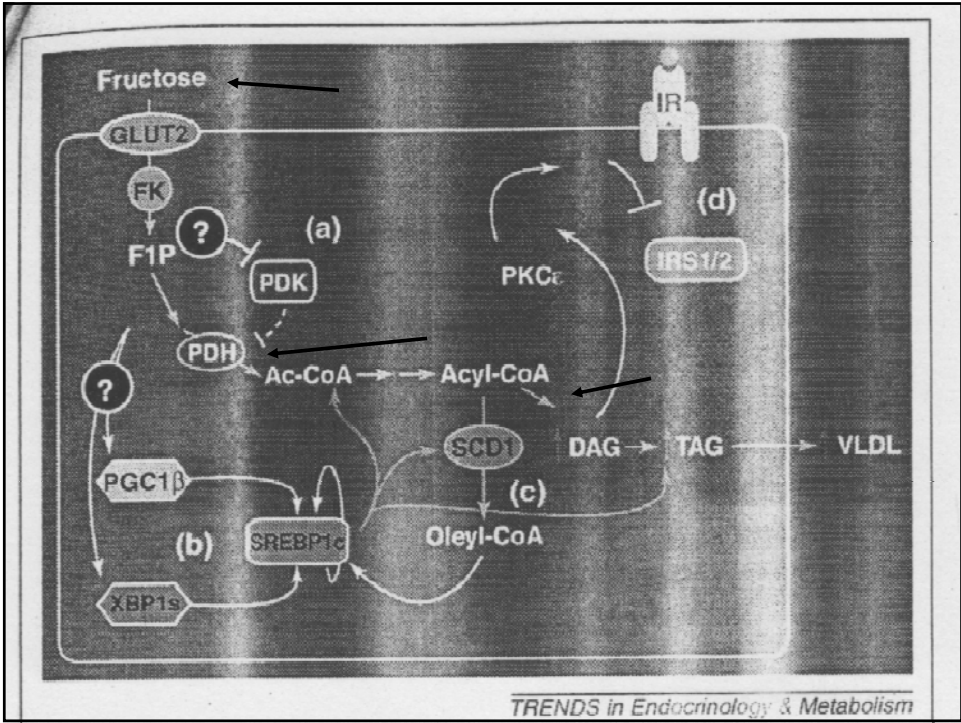
consumption is attributable to increased consumption of beverages that are sweetened with HFCS; and some have suggested that the use of HFCS might have indirectly contributed to this increase [3]. HFCS is denser than cane sugar, allowing manufacturers to use the sweetener from production to better the rise in food prices [4]. This net increase in consumption might not appear significant at first, as a population, we consume ~50 grams per day; then we did three decades ago, roughly the amount of sugar contained in 1.5 cans of a regular soda drink [1]. But considering that this equates to an increased caloric consumption

of ~18 kg per capita, the contribution to the obesity epidemic becomes more apparent. Although these numbers are useful for discussing our collective behavior, fructose consumption is not uniform across the population; consumption varies greatly between the lowest and highest consumers, the latter exemplified by adolescent males, who consume the greatest amount of fructose (estimated between 3.5-5.5 g/kg body weight per day) [1].

Corresponding author: Samuel, V.T. (samuel@yale.edu)

doi:10.1016/j.tcm.2011.01.001 Published by Elsevier Ltd. 1873-7922/\$ - see front matter. Published by Elsevier Ltd. 1873-7922/\$ - see front matter. Published by Elsevier Ltd. 1873-7922/\$ - see front matter.

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European Journal of Clinical Nutrition (2011) 65, 1173–1189
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REVIEW

Obesity and energy balance: is the tail wagging the dog?

JCK Wells¹ and M Siervo²

¹Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK and ²Human Physiology and Nutrition Unit, Department of Neuroscience, Faculty of Medicine, University Federico II of Naples, Naples, Italy

The scientific study of obesity has been dominated throughout the twentieth century by the concept of energy balance. This concept, based on fundamental thermodynamic principles, states that energy cannot be destroyed, and can only be gained, lost or stored by an organism. Its application in obesity research has emphasized excessive appetite (gluttony), or insufficient physical activity, as the primary causes of weight gain. However, this model cannot explain why weight accumulates persistently rather than reaching a plateau, and underplays the effect of variability in dietary constituents on energy and intermediary metabolism.

Wells JCK & Siervo M. Obesity and energy balance: is the tail wagging the dog? *Eur J Clin Nutr*, Vol. 65, No. 11, pp. 1173-1189, November 2011.

European Journal of Clinical Nutrition (2011) 65, 1173–1189. doi:10.1038/ejcn.2011.122; published online 20 July 2011

Keywords: fructose; obesity; metabolism; energy balance; metabolic flexibility

Introduction

This review discusses the role of fructose in obesity and energy balance, and the effect of variability in dietary constituents on energy and intermediary metabolism.

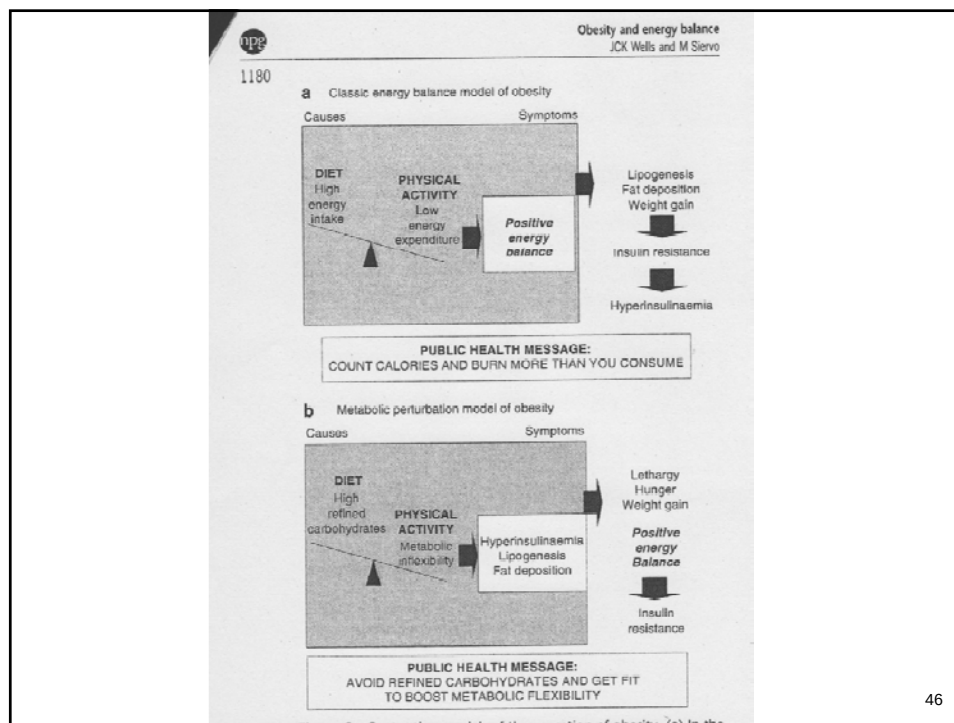
Obesity is a global health problem, with prevalence increasing rapidly in many countries. The scientific study of obesity has been dominated throughout the twentieth century by the concept of energy balance. This concept, based on fundamental thermodynamic principles, states that energy cannot be destroyed, and can only be gained, lost or stored by an organism. Its application in obesity research has emphasized excessive appetite (gluttony), or insufficient physical activity, as the primary causes of weight gain. However, this model cannot explain why weight accumulates persistently rather than reaching a plateau, and underplays the effect of variability in dietary constituents on energy and intermediary metabolism.

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- “An alternative model emphasises the capacity of fructose and fructose-derived sweeteners (sucrose, high-fructose corn syrup) to perturb cellular metabolism...which favour[s] adipose tissue accretion and increased appetite while depressing physical activity.”
- “This model implicates chronic hyperinsulinaemia in the presence of a paradoxical state of ‘cellular starvation’ as a key driver of the metabolic modifications inducing chronic weight gain.”

45



Pyridoxine (Vitamin B6)

47

[illegible]

- **“Low plasma concentrations of the vitamin B-6 form of pyridoxal 5'-phosphate (PLP) have been reported in patients with high levels of inflammatory markers and with conditions associated with inflammation, including rheumatoid arthritis, cardiovascular disease, and diabetes.”**

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- **“...in patients with an inflammatory condition like rheumatoid arthritis, erythrocyte PLP seems to be a measure of vitamin stores restricted to the erythrocyte compartment, and plasma PLP may be a better indicator of overall vitamin B-6 status.”**

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- **“We...demonstrated in this study population of patients with coronary artery disease that inflammation is the main predictor of impaired vitamin B-6 status, and 94% of the participants with PLP below the 5th percentile had increased concentrations of 1 or several markers of inflammation.”**

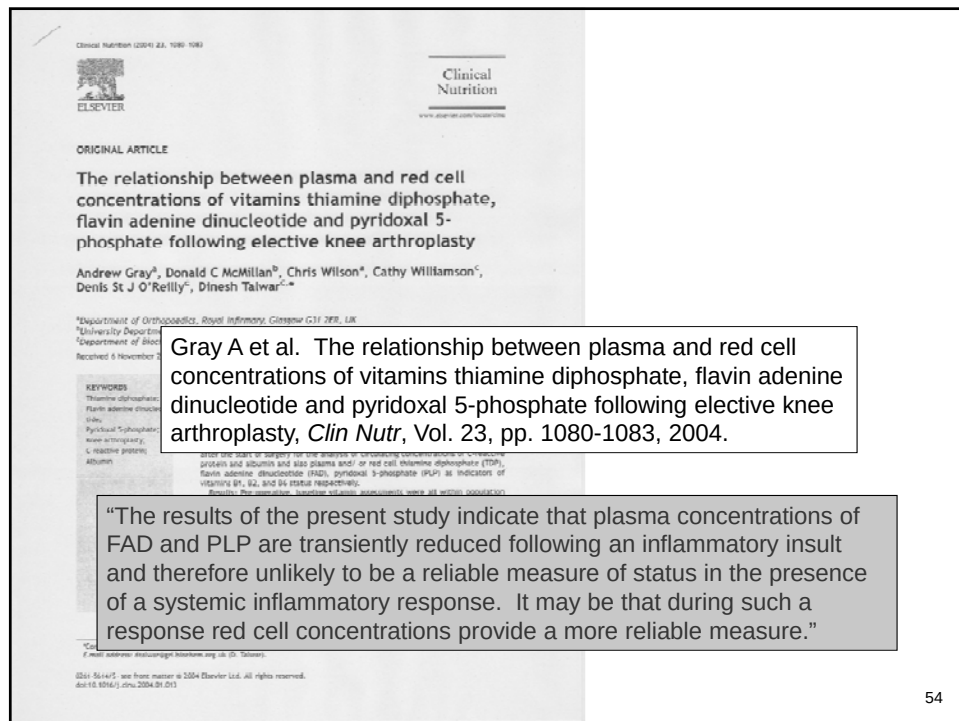
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- **“Our data confirm published reports on an association between elevated CRP and low PLP in healthy individuals and patients with inflammatory conditions, including CVD.”**
- **“Vitamin B-6 depletion during inflammation and immune activation may be related to the involvement of PLP in cytokine production and lymphocyte proliferation.”**

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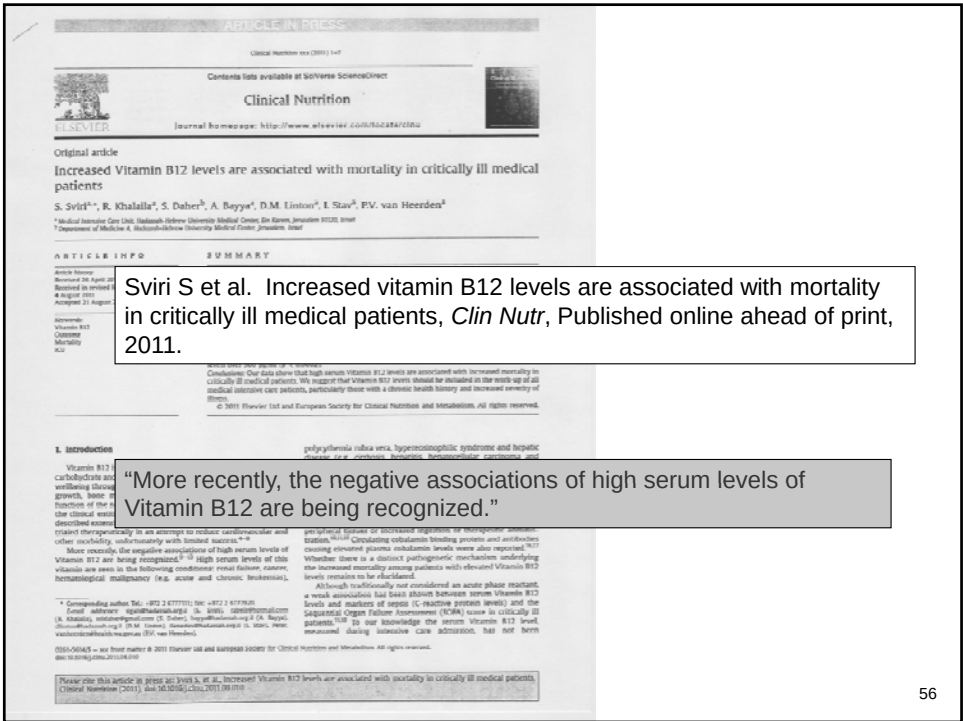
- “...pyridoxine supplementation did not affect the plasma concentration of any of the inflammatory mediators.”

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Vitamin B12

55



- “High serum levels of this vitamin are seen in the following conditions: renal failure, cancer, hematological malignancy (e.g. acute and chronic leukemias), polycythemia rubra vera, hypereosinophilic syndrome and hepatic disease (e.g. cirrhosis, hepatitis, hepatocellular carcinoma and metastatic liver tumors.”

57

- “Although traditionally not considered an acute phase reactant, a weak association has been shown between serum Vitamin B12 levels and markers of sepsis (C-reactive protein levels)...”
- “Vitamin B12 levels were also positively correlated with severity of illness...”
- “Decreased intracellular cobalamin levels may parallel increased plasma levels.”

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“In the present study, a strong positive correlation was found between uMMA and hs-CRP in patients with acute myocardial infarction.”

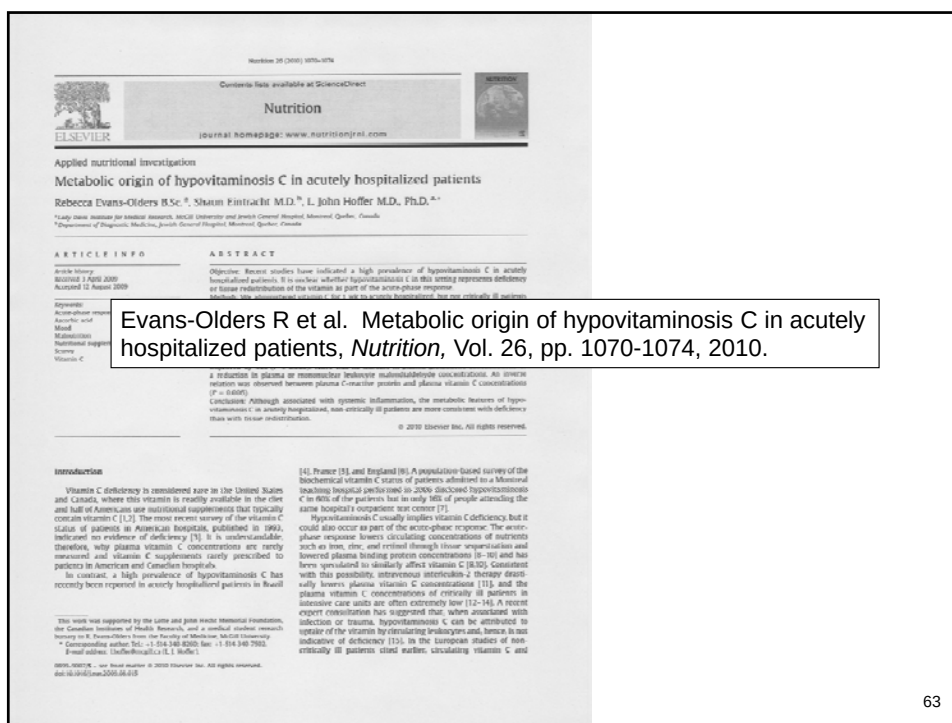
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Vitamin C

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- **“Hypovitaminosis C usually implies vitamin C deficiency, but it could also occur as part of the acute phase response.”**
- **“In the European studies of non-critically ill patients cited earlier, circulating vitamin C and C-reactive protein (CRP) concentrations were inversely related, suggesting that the acute-phase response could indeed account for the hypovitaminosis C observed in this setting.”**

- **“In agreement with previous reports, baseline CRP concentrations were inversely related to plasma vitamin C concentrations. In light of the present findings and previous observations, it is reasonable to suggest that systemic inflammation increases vitamin C catabolism, but induces deficiency only when vitamin C intake is inadequate .”**

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- **“Congruent with this possibility, there is evidence that cigarette smoking increases vitamin C turnover, reduces plasma vitamin C concentrations, and increases the dietary vitamin C requirement. The same mechanism could act even more strongly in acutely hospitalized patients.”**

66

Vitamin C and sickness behavior

- **“There is a well-known but little-studied relation between vitamin C deficiency and affective state. It is not surprising that such a relation exists, because vitamin C is involved in neuronal transmission and neurotransmitter metabolism, and its cerebrospinal fluid concentration is approximately three-fold higher than, and tightly linked to, its plasma concentration.”**

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- **“Vitamin C therapy increased plasma ($P < 0.0001$ and mononuclear leukocyte ($P = 0.014$) vitamin C concentrations and was associated with a 34% reduction in mood disturbance ($P = 0.013$).”**

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- **“Hypovitaminosis C usually implies vitamin C deficiency, but the response to systemic inflammation could redistribute the vitamin into leukocytes or other tissues, without necessarily indicating nutritional deficiency. It is also possible, however, that systemic inflammation increases vitamin C catabolism and induces true biochemical deficiency when vitamin C provision is inadequate.”**

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- ***“Indeed, whether hypovitaminosis C is caused by redistribution of the vitamin into tissues, increased catabolism, or both, a predictable consequence is reduced vitamin C availability to the brain.”***

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Micronutrients and chronic illness: The big picture

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Clinical Nutrition 30 (2011) 478–483

Contents lists available at ScienceDirect

Clinical Nutrition

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

Original Article

Higher plasma pyridoxal 5'-phosphate is associated with better blood glucose responses in critically ill surgical patients with inadequate vitamin B-6 status

Chen-Tai Hou^{a,*}, Ying-Hsun Wu^b, Pei-Ning Huang^c, Chien-Hsiang Cheng^d, Yi-Chia Huang^{e,*}

^a Critical care, Changhua Christian Hospital, Changhua, Taiwan, ROC
^b Burn Center, Changhua Christian Hospital, Changhua, Taiwan, ROC
^c Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan, ROC
^d Department of Surgery, Changhua Christian Hospital, Changhua, Taiwan, ROC
^e School of Medicine, Changhua Christian Hospital, Changhua, Taiwan, ROC

ARTICLE INFO

Article history:
Received 12 July 2010
Accepted 20 August 2010

Keywords:
Vitamin B-6
Pyridoxal 5'-phosphate
Glucose
Insulin
Surgery

Abstract

Background: Hypovitaminosis B-6 is common in critically ill patients, even in those without diabetes mellitus, and has been shown to be associated with increased morbidity and mortality.^{1–3} van den Berghe et al.^{4,5} had suggested tight glucose control (<150 mg/dL) with increased utilization of insulin results to reduce mortality rates in surgical critically ill patients. However, achieving normal levels of blood glucose can be hazardous to patients in the intensive care unit (ICU), and tight glucose control remains controversial. Studies have indicated that increased insulin administration could be positively associated with death^{6–10} and might cause hypoglycemia^{11–13} in the ICU. A recent large multicenter trial (NICE-SUGAR study)¹⁴ concluded that a goal

Hou CT et al. Higher plasma pyridoxal 5'-phosphate is associated with better blood glucose responses in critically ill surgical patients with inadequate vitamin B-6 status, *Clin Nutr*, Vol. 30, No. 4, pp. 478-483, August 2011.

“Stress, inflammation, and clinical conditions may increase the utilization and metabolic turnover of vitamin B-6 and lower the body pool of vitamin B-6.”

1. Introduction

Hypovitaminosis B-6 is common in critically ill patients, even in those without diabetes mellitus, and has been shown to be associated with increased morbidity and mortality.^{1–3} van den Berghe et al.^{4,5} had suggested tight glucose control (<150 mg/dL) with increased utilization of insulin results to reduce mortality rates in surgical critically ill patients. However, achieving normal levels of blood glucose can be hazardous to patients in the intensive care unit (ICU), and tight glucose control remains controversial. Studies have indicated that increased insulin administration could be positively associated with death^{6–10} and might cause hypoglycemia^{11–13} in the ICU. A recent large multicenter trial (NICE-SUGAR study)¹⁴ concluded that a goal

* Corresponding author. Tel.: +886 4 2473002x27188; fax: +886 4 27348175.
E-mail address: yeh@ccu.edu.tw (Y.-C. Huang).

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doi:10.1016/j.clnu.2010.08.014

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- “Pyridoxal 5'-phosphate (PLP), the physiological active coenzyme form of vitamin B-6, is involved in gluconeogenesis and glycogenolysis through its role in transaminase reactions and in the action of glycogen phosphorylation.”
- “Decreased vitamin B-6 concentrations were observed in diabetic animals and patients, and there was a significant association between glucose intolerance and vitamin B-6 deficiency in rats.”

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ORIGINAL COMMUNICATION

Vitamin B6 intakes and status of mechanically ventilated critically ill patients in Taiwan

Y-C Huang¹*, F-J Lan¹, C-H Cheng², B-J Lee³ and M-N Kan³

¹School of Nutrition, Chung Shan Medical University, Taiwan, Republic of China; ²Critical Care and Respiratory Therapy, Taiwan, Republic of China; and ³Intensive Care Unit, Taichung Veterans General Hospital, Taichung, Taiwan, Republic of China

Objective: To assess vitamin B6 intake and status of critically ill patients. The relationship between vitamin B6 status (PABP/PLP) and the severity of illness and outcome in these patients was also examined.

Design: Prospective clinical study.

Setting: The study was performed at the Taichung Veterans General Hospital, in the central part of Taiwan.

Subjects: Ninety-four patients in the intensive care unit (ICU) entered the study and 46 patients successfully completed this

Huang YC et al. Vitamin B6 intakes and status of mechanically ventilated critically ill patients in Taiwan, *Eur J Clin Nutr*, Vol. 56, pp. 387-392, 2002.

decreased at the 14th day after admission ($P < 0.05$). Erythrocyte aspartate aminotransferase activity coefficient and EAST-AC did not change significantly. Urinary 4-PH significantly increased at the 14th day ($P < 0.001$). No significant relationships were found between AWP/PE, S scores and clinical outcome (the length of ICU and hospital stay, the length of ventilation dependent).

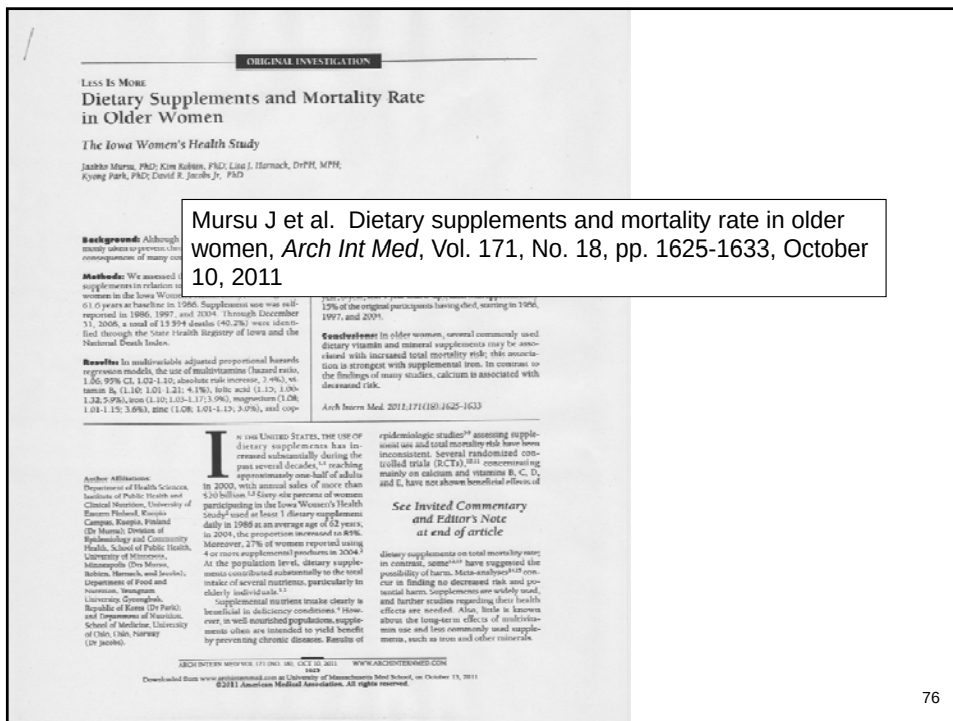
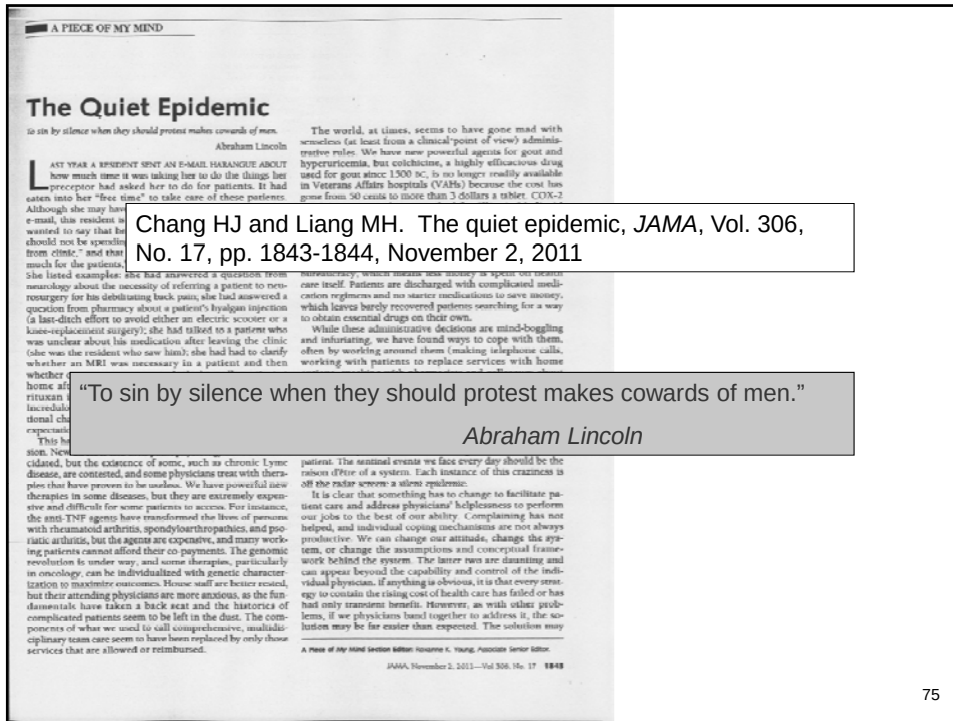
“Patients had an adequate mean vitamin B6 intake (16.26 ± 19.39 mg) during the 14 day study. Mean vitamin B6 intake was significantly higher on day 14 than on day 1”

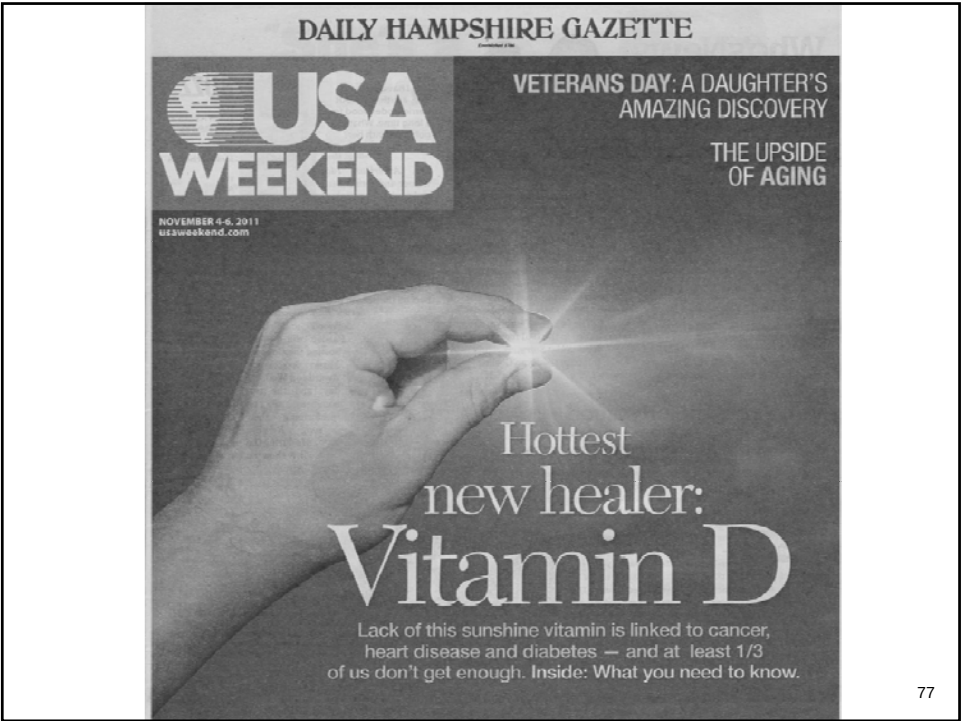
Keywords:

“...we noted that plasma pyridoxal 5'-phosphate (PLP) and pyridoxal (PL) concentrations significantly decreased while vitamin B6 intake significantly increased on day 14. Critical clinical conditions and complex metabolism in the critically ill may account for the reduction of plasma PLP and PL.”

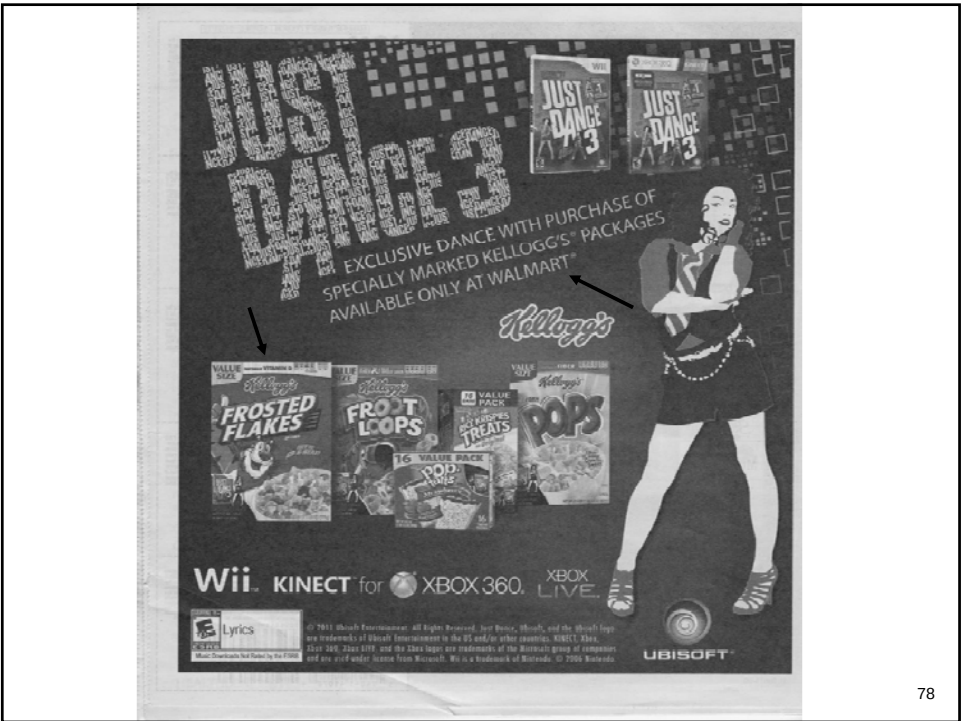
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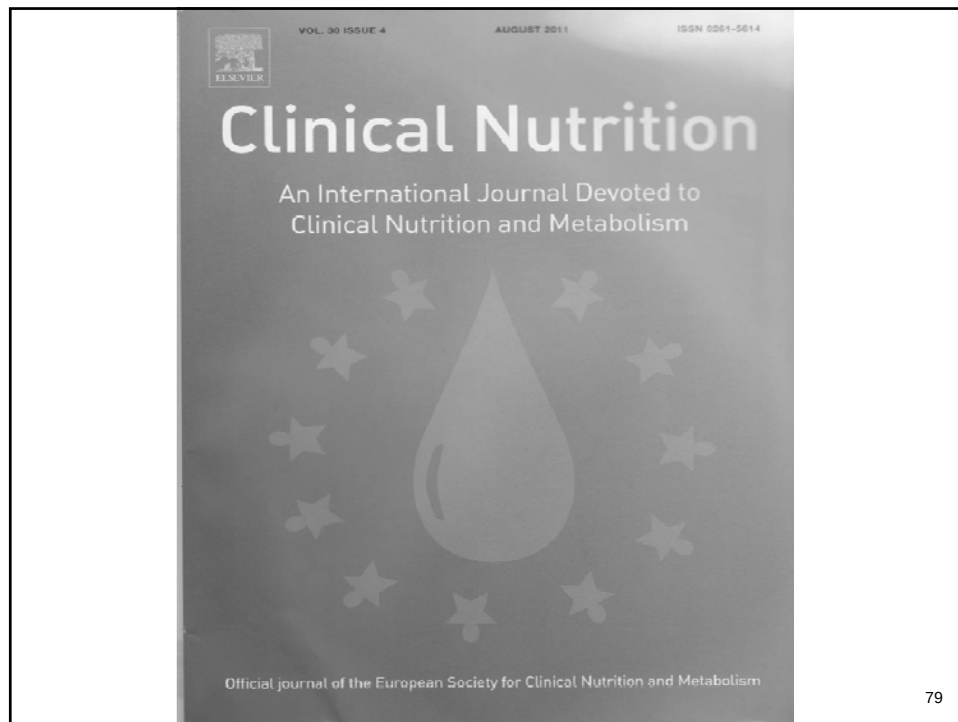




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With the above in mind, how
should we proceed with
micronutrient supplementation
with chronically ill patients?

Supplement using amounts
based on patient need rather
than RDA/RDI dogma

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PLUS

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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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Thank you!!