Using organic acids to resolve chief complaints and improve quality of life in chronically ill patients

Part X

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Sulfur metabolism – Part I:
The impact of chronic inflammation and chronic illness
Summer of work exposes medical students to system’s ills. The New York Times, September 9, 2009

“...a tidal wave of chronic illness...”

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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<th>Considerations for the Catabolic Patient</th>
<th>Key deficiencies or excesses, i.e., Calories, macronutrients, B vitamins, zinc, selenium, iodine, sleep, psychological and chemical stress, movement against gravity, weight</th>
<th>Low calorie intake and excessive carbohydrate/protein ratio – Refeeding syndrome</th>
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**THE CREATION OF THE EXCESSIVE CATABOLIC PHYSIOLOGY “RESPONSE”**
Sulfur metabolism:
The metabolic “big picture”

USA Today, October 16, 2011

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Sulfur metabolism:
Basic biochemistry and physiology

• “Homocysteine exists at a metabolic branch point in that it can be remethylated back to methionine, or can be irreversibly catabolized via the transsulfuration pathway to generate cystathionine and subsequently cysteine.”
• “Mudd and Poole demonstrated that approximately half of the homocysteine is metabolized by transsulfuration to cystathionine and the other half is remethylated back to methionine.”

• “Methionine is the primary donor of methyl groups, in the form of S-adenosylmethionine (SAM), for biological methylation reactions.”
• “Following all SAM-dependent transmethylation reactions, S-adenosylhomocysteine (SAH) is generated, which is a potent inhibitor of most methyltransferases.”
• “Because SAM is a positive modulator of methyltransferase activity, the intracellular ratio of SAM to SAH is considered an index of transmethylation potential.”
"...cysteine can be converted to pyruvate and inorganic sulfate as a means to meet energy needs by gluconeogenesis and remove sulfur from the body via the urine, respectively."

Information on SAM

- "SAM inhibits the activity of methyltetrahydrofolate reductase (MTHFR) allosterically, thereby reducing 5-CH3THF production..."
- "SAM-dependent methyltransferase reactions include the synthesis of carnitine from lysine, the activation and inactivation of neurotransmitters, and the methylation of DNA for epigenetic control of gene expression."

Impact of high protein diet

- "In brief, the excess methionine is activated to SAM, which exerts its allosteric control on methyltransferases, MTHFR, and cystathionine beta-synthase (CBS)."
- "Collectively, this results in the increased catabolism of methionine through the transmethylation and transsulfuration pathway, diminishes methionine generation by homocysteine remethylation, and disposes of excess methyl groups."
“Thyroid status, both hyper- and hypothyroidism, has been shown to perturb both the hepatic folate-dependent one-carbon pool and regulatory proteins involved with sulfur amino acid metabolism...”

Sulfur metabolism: The impact of chronic inflammation
• “...when the diet is low in sulfur amino acids cellular methionine is highly conserved.”

• “Flux down the transsulfuration pathway, which ultimately leads to methionine catabolism, increases only as dietary methionine intake increases.”

How does the body respond to environmental stressors?

• “The immune system has great capacity for immobilizing invading microbes, creating a hostile environment for them and bringing about their destruction.”

• “It can also become activated, in a similar way to the response to microbial invasion, by a wide range of stimuli and conditions.”
• “These include burns, penetrating and blunt injury, the presence of tumor cells, environmental pollutants, radiation, exposure to allergens, and the presence of chronic inflammatory diseases.”

• “The strength of the response to this disparate range of stimuli will vary, but it will contain many of the hallmarks of the response to invading pathogens.”

• “The immune response has a high metabolic cost, and inappropriate prolongation of the response will exert a deleterious effect on the nutritional status of the host.”

What happens to sulfur with chronic illness?

• “Infection with human immunodeficiency virus (HIV)…has been shown to cause substantial excretion of sulfate in the urine during the asymptomatic phase of the disease.”

• “The losses reported were equivalent to 10 g of cysteine per day, in contrast to losses of approximately 3 g/d for healthy individuals on a ‘Westernized diet.’”

• “Large decreases in plasma glycine, serine, and taurine concentrations occur following infection and injury.”

• “These changes may be due to enhanced utilization of a closely related group of amino acids, namely glycine, serine, methionine, and cysteine.”
• “Many substances produced in enhanced amounts in response to pro-inflammatory cytokines are particularly rich in these amino acids.”
• “These substances include GSH (composed of glycine, glutamic acid, and cysteine), metallothionein (the major zinc transport protein), in which glycine, serine, cysteine, and methionine make up 56% of the total amino acids, and a range of acute phase proteins which contain up to 25% of these amino acids in their structure.”

“If an increased demand for sulfur and related amino acids is created by the inflammatory response then provision of additional supplies of these amino acids may assist the response.”

Sir David Cuthbertson: The father of research on the impact of illness on nutritional status

Ebb and flow

• “Cuthbertson followed his initial observations on the metabolic response to injury by dividing the response into the early or ‘ebb’ phase of depressed vitality lasting for a day or so, and followed by resurgence of vitality which he termed the ‘flow’ phase and which seemed to bear a certain resemblance to inflammation.”

• “The flow phase can be divided into a catabolic phase, lasting days to weeks, and the later anabolic phase, lasting weeks to months.”

• “The catabolic response to injury and infection is characterized not only by weight loss and weakness, but resting hypermetabolism, increased nitrogen excretion, carbohydrate intolerance and increased mobilization of fat.”
Figure 3. A schematic diagram is used to emphasize the pathways which are available for muscle but unavailable for liver in the presence of severe infections.
“More recently the present author has investigated, in part, the effect of tissue injury on metabolism.”

“It was found that the urinary excretion of sulphur, nitrogen and phosphorus rose rapidly to a maximum generally within 3 to 6 days from the time of injury.”

“The S:N ratio suggested that some sulphur-rich tissue, such as muscle, might be the main source of the material catabolised.”

“It is obvious in the first place that the source of these nitrogen and sulphur losses cannot be food intake. They must come from the increased catabolic changes in the tissue cells and body fluids.”

“Urea and inorganic sulphate are the chief products of increased endogenous catabolism.”
The impact of prolonged immobilization

• “Those subjected showed, within a day or two from the commencement period of prolonged rest, a rise in urinary excretion of sulfur (S), N, P and, to a lesser extent, of Ca (in order of priority).”
• “The rise in N excretion was due to a practically proportionate increase in the excretion of urea; that of S was due to a practically proportionate excretion of inorganic sulphate…”


“The growth suppression associated with environmental enteropathy is believed to result from repartitioning of dietary nutrients away from pathways that result in growth, toward processes related to host defense and catabolism.”
• “In environments of poor sanitation, where chronic and recurrent infections are common, we propose that increased oxidative stress drives methionine influx toward cystathionine production.”
• “This ‘cystathionine siphon’ limits remethylation of homocysteine, a process that intersects with a cellular proliferation pathway.”

• “The principle of a ‘cystathionine siphon’ is illustrated by experimental data in humans demonstrating that even a mild inflammatory challenge such as immunization can drive methionine flux towards cystathionine.”
• “…Mercer et al. showed an increased ratio of transulfuration to transmethylation and decreased ratio of remethylation 2 days following vaccination.”

• “Increased cystathionine β-synthase (CBS) activity could be one mechanism for our proposed ‘cystathionine siphon.’”
• “Both lipopolysaccharide and TNFα are known to increase CBS activity in vivo.”
• “Enterocytes have a rapid turnover. Therefore, a decrease in protein synthesis is likely to negatively impact cell proliferation and function, and could lead to failure of the intestinal barrier.”
“Further, limiting dietary sulfur amino acids preferentially affects the jejunal mucosa.”

Organic Acids – Part 10
Dr. Jeff Moss

• “The amino acids needed for the synthesis of compounds and proteins involved in host defence may be different from those provided by muscle proteolysis, leading to an excessive mobilization of muscle proteins until the appropriate amount of the most limiting amino acid is reached.”

• “Preston et al estimated that the synthesis of 1 g fibrinogen would require the degradation of 2.6 g muscle protein.”

• “The synthesis of cysteine from methionine has been found to increase 2.7 fold 2 days after infection in rats.”

• “Taken together, these results indicate an increased cysteine requirement in diseases.”

• “…catabolic states and chronic diseases are generally associated with the depletion of glutathione pools…”

• “It is well established that the acute phase response leads to important metabolic changes in general and in protein and amino acid metabolism in particular, i.e., the metabolism of individual amino acids, especially methionine and cysteine.”
• “Injury, the contribution of the transsulfuration pathway to methionine flux increases, which suggests an increased cysteine requirement in diseases.”

• “The preferential methionine metabolism toward cysteine synthesis observed after vaccination suggests an increased requirement of sulfur amino acids even in mild inflammatory situations.”
• “The main finding of this study is a higher proportion of methionine entering the transsulfuration pathway in elderly subjects before vaccination.”

“Inflammation and oxidative stress were found to activate the methionine cycle and transsulfuration, which allowed an increased cysteine availability for glutathione synthesis.”
• “The metabolic results indicated that plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), an indicator or methylation capacity, were significantly decreased in the autistic children relative to age-matched controls.”

• “In addition, plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox status, were significantly decreased.”

• “Differences in allele frequency and/or significant gene-gene interactions were found for relevant genes encoding the reduced folate carrier (RFC 80G>A), transcobalamin II (TCN2 776G>C), catechol-O-methyltransferase (COMT 472G>A), methylenetetrahydrofolate reductase (MTHFR 677C>T and 1298 A>C), and GSTM1.”
• “The results of this study demonstrate for the first time that some parents of children with autism exhibit significant metabolic deficits in methylation capacity (↓SAM/SAH) and in glutathione-mediated antioxidant and detoxification capacity (↓GSH/GSSG).”

• “In summary, we have discovered a significant metabolic imbalance in transmethylation and transsulfuration pathways in many parents that is similar to the imbalance previously observed in many autistic children.”

• “A decrease in the GSH/GSSG redox ratio has been associated with several genetic polymorphisms, chronic dietary deficiencies, and pro-oxidant environmental exposures.”

• “Glutathione can also be decreased by chronic psychological stress and severe anxiety.”

• “The two pathways of transmethylation and transsulfuration are metabolically interdependent such that chronic deficit in glutathione will feed back to inhibit SAM synthesis and create a chronic self-perpetuating cycle that progressively decreases GSH levels.”
“The fact that both pathways were adversely affected in many parents suggests that the initiating factors were chronic in nature.”


“The intervention trial was effective in normalizing the metabolic imbalance in the autistic children.”

Folinic acid, Betaine, Injectable methylcobalamin

“Although clinical improvements in speech and cognition were noted by the attending physician, they were not measured in a quantifiable manner and are therefore not reported here.”

Thank you!!