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

Part XI

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The goal: to wean doctors off procedures that don’t necessarily benefit patients.
Sulfur metabolism – Part II:
Diagnostic modalities
and metabolic correction

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.”
Organic Acids – Part 11

Dr. Jeff Moss

Key deficiencies or excesses, i.e.,
Calories, macronutrients, B vitamins, zinc, selenium, iodine, sleep, psychological
and chemical stress, movement against
gravity, weight

Chronic inflammation,
inflammaging

Low calorie intake
and excessive
carbohydrate/protein
ratio – Refeeding
syndrome

Hyperinsulinemia/insulin
resistance

Sarcopenia/loss of lean
body mass

Low grade chronic
metabolic acidosis/fluid
electrolyte imbalance

Gut
dysfunction/atrophy

THE CREATION OF THE EXCESSIVE CATABOLIC
PHYSIOLOGY “RESPONSE”

Table 1: Overlapped symptoms of acute sickness behaviors as
associated with HPA axis activation and the somatic symptoms in
MDD

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Presence in %</th>
<th>Presence in MDD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/arthria</td>
<td>75</td>
<td>73</td>
</tr>
<tr>
<td>Headache</td>
<td>7%–67%</td>
<td>31%–69%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>50–75%</td>
<td>24–47%</td>
</tr>
<tr>
<td>Pharyngitis/sores</td>
<td>46%–49%</td>
<td>29–62%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>36%–19%</td>
<td>63</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>19%</td>
<td>59</td>
</tr>
<tr>
<td>Anxiety</td>
<td>19–38%</td>
<td>31%–49%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26–35%</td>
<td>63%–88%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15–28%</td>
<td>21%–61%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12–27%</td>
<td>49</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11–18%</td>
<td>47</td>
</tr>
<tr>
<td>Peak concentration</td>
<td>14%–15%</td>
<td>51</td>
</tr>
</tbody>
</table>

1 [49], unless otherwise specified.
2 [90], unless otherwise specified.
3 [101], [102], [103], [104], [105].
4 Feeling terted, bowel problems.
5 Result from depressed control population.

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Sulfur metabolism:
The metabolic “big picture”


Diagnosis of glutathione status: 
α-Hydroxybutyrate
• “Although there is little direct evidence to date, the dominant source of urinary α-hydroxybutyrate (AHB) seems to be the conversion of cystathionine to cysteine.”
• “The activity of this pathway is highly variable, changing in response to demands for protection against oxidative stress.”
• “As oxidative stress increases, the flow of homocysteine shifts away from transmethylation to methionine toward transsulfuration to cystathionine in order to increase the flux of cysteine into glutathione synthesis.”

“Thus, AHB production can be directly related to the rate of hepatic glutathione synthesis.”

Clinical conditions associated with elevated urinary AHB

• Smoking
• Poor diet
• Lack of exercise
• Infectious diseases such as measles
• Birth asphyxia
“All of the conditions that have been associated with increased AHB excretion may be related to increased rates of hepatic glutathione synthesis from methionine.”

“When the conversion is limited by availability of methionine (and homocysteine) the lower rate of glutathione production can be reflected by falling AHB in urine.”
• “Elevated AHB, thus, shows increased flow through the transsulfuration pathway as required during times of increased demand for glutathione for meeting oxidative stress or for detoxification functions.”
• “Other signs, such as urinary pyroglutamate and sulfate...must be assessed to determine a patient’s ability to sustain this flow.”

• “It is also possible to find some patients in late stages of chronic glutathione and methionine depletion who have such a low capacity to generate the transsulfuration flow that their AHB is normal.”
• “These patients generally show low plasma methionine and taurine.”

Diagnosis of glutathione status:
Pyroglutamate
• “Pyroglutamate is created in the γ-glutamyl cycle (GGC), a pathway that is highly active in renal tubules and anywhere there is a high demand for glutathione.”

• “In healthy individuals, a very modest amount of pyroglutamate is spilled in the urine because the rate of pyroglutamate conversion to glutamate for glutathione reformation keeps pace with the rate of γ-glutamyl amino acid formation.”

• As glutathione fails to be recovered in the γ-glutamyl pathway, a concurrent reduction in total body sulfate may be found.

• “Studies showing an age-related decline in expression of glutathione synthesis in rat liver suggests that this problem may be more prevalent in older patients.”

• “If any compromise in energy production occurs, an increase in pyroglutamate could theoretically be noted.”
• “Alternatively, drugs that require glutathione conjugation can cause failure to sustain glutathione adequacy. This effect has been reported with acetaminophen toxicity.”
• “Burn patients excrete higher than normal amounts of pyroglutamate, whereas their blood levels of glutathione are lowered and their rate of glycine synthesis is decreased.”

• “Urinary pyroglutamic aciduria has been reported as a marker for glycine deficiency.”
• “If glycine conjugation demand concurrently is increased in healthy human subjects by methionine loading, then pyroglutamate excretion increases because of lowered availability of glycine.”
• “Under these conditions urinary pyroglutamate is positively related to urinary sulfate in a linear manner over the entire sulfate concentration range.”

• “Small amounts of pyroglutamate are always present in overnight urine because it is produced as an intermediate in a cycle used in the active transport of amino acids in renal tubules.”
• “Since the appearance of a micromole of pyroglutamate in urine is accompanied by the recovery of a micromole of amino acids into the renal blood supply, we might think of the situation as one where glutathione is wasted in order to prevent massive essential amino acid loss.”
“Up to one-third of the glutathione circulating in blood may be used in this amino acid recovery process.”

“Since pyroglutamate may be formed by heating of foods that contain high amounts of glutamic acid, urinary pyroglutamate may have dietary origins.”

“Foods high in glutamic acid include artificial diets where glutamate is used as a flavor enhancer and high-protein foods, such as meats, eggs, and dairy products.”

Diagnosis of glutathione status:
Sulfate
"Sulfate is the ionic form of an inorganic rather than organic acid."

"It may be included on panels of urinary organic acids because of the important information it provides about sulfur metabolism."

"For example, the protein synthesis disruption of zinc deficiency causes decreased incorporation of cystine into proteins with concurrent large increases in urinary sulfate and taurine from cysteine degradation."

"The rise in sulfate parallels the depth of zinc deficiency, indicating that, if other sulfate sources are normalized, urinary sulfate can be a metabolic marker of the severity of zinc deficiency."

"Severe depletion of organic sulfur sources will cause simultaneous high pyroglutamate and low sulfate excretion."

"High pyroglutamate with normal sulfate indicates inadequate organic sulfur sources for production of cysteine required for glutathione synthesis."

"Only organic sulfur in the form of compounds such as N-acetylcysteine or methionine along with adequate glycine will restore normal glutathione levels."
• “Normal urinary pyroglutamate with low sulfate levels can occur in individuals with impaired sulfate activation.”
• “In these cases, rapid replenishment of hepatic sulfate may be accomplished with either sulfur donors like N-acetylcysteine or inorganic sulfate such as sodium sulfate.”
• “On the other hand, a well nourished patient under temporary metabolic stress of detoxification from, for example, use of acetaminophen, may have elevated α-hydroxybutyrate, signaling the increased rate of hepatic glutathione synthesis, but have no need for amino acid or glutathione therapy due to normal sulfate level.”

• “An individual with limited ability to produce glutathione may show the glycine depletion sign of high pyroglutamate and low sulfate.”
• “This patient is a candidate for glutathione administration along with glycine and N-acetylcysteine or methionine, and their taurine status should be monitored, since depletion of other sulfur-containing compounds is likely.
• “Urinary sulfate has also been shown to reflect intake of sulfiting agents widely used as food additives.”

Treatment options for optimizing glutathione status

“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.”
Optimize anabolic/catabolic balance via Entry Level Clinical Nutrition

Considerations for the Catabolic Patient

Key deficiencies or excesses, i.e., Calories, macronutrients, B vitamins, zinc, selenium, iodine, sleep, psychological and chemical stress, movement against gravity, weight

Low grade chronic metabolic acidosis/fluid electrolyte imbalance

Sarcopenia, loss of lean body mass

Chronic inflammation, inflamming

Low calorie intake and excessive carbohydrate/protein ratio – Refeeding syndrome

Hyperinsulinemia/Insulin resistance

Gut dysfunction/atrophy

THE CREATION OF THE EXCESSIVE CATABOLIC PHYSIOLOGY “RESPONSE”
Supplementation


• "A number of strategies have evolved to raise levels of glutathione in depleted individuals."
• "There are at least three potential ways of enhancing cellular GSH content: administration of the three amino acids (cysteine, glutamic acid, and glycine) which comprise the tripeptide, either singly or in various combinations; administration of cofactors for the metabolic pathways leading to GSH production, that is, vitamin B6, riboflavin, and folic acid; and administration of synthetic compounds which become converted to precursors of GSH."
• “In HIV positive patients a whey protein formulation was clearly demonstrated to increase plasma GSH concentrations.”

• “N-acetyl cysteine (NAC) rapidly enters the cell and is speedily deacylated to yield L-cysteine.”

• “…randomized studies on asymptomatic HIV positive patients in the presence and absence of antiretroviral therapy (ART) have shown that NAC can raise blood GSH, increase natural killer cell activity, and enhance stimulation indices of T cells incubated with mitogen or tetanus toxin.”

• “Interestingly the rise in T cell function was accompanied by a fall in plasma IL-6 in subjects receiving ART as well as the drug.”

• “Furthermore studies have shown that survival time was improved in HIV+ patients who maintained high concentrations of GSH in CD4+ T lymphocytes.”

• “It could therefore be surmised that improved T cell function and reduced inflammation are modulated by improvement in antioxidant status in these patients.”

• “Alpha-lipoic acid provides a further means of enhancing tissue GSH content.”

• “The compound is reduced to dihydrolipoic acid, which converts cystine to cysteine.”

• “Cysteine, on gaining entry to the immune cells, is rapidly converted to GSH.”

• “Flow cytometric analysis of freshly prepared human peripheral blood lymphocytes shows that lipoic acid is able to normalize a subpopulation of cells with severely compromised thiol status rather than increasing the level in all cells above normal values.”
“Hence lipoic acid may also prove to be a useful clinical agent for restoring cellular GSH concentrations in immunocompromised subjects.”


“N-acetylcysteine (NAC) is an effective oral agent for rebuilding total body glutathione, and oral taurine spares sulfur amino acids while providing an effective antioxidant.”
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Dosing recommendations

- N-acetylcysteine – 1500 mg/day with meals
- Lipoic acid – 300 mg/day with meals
- R-lipoic acid – 150 mg/day with meals
- Taurine – 1-2 g per day with meals

Thank you!!