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

Part III

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

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“...a tidal wave of chronic illness...”
• “Cachexia may well represent the devastating flip side of the tremendous achievements of modern medicine, as the incidence of cachexia is also a function of survival of chronic illness.”

• “Many diseases – which rapidly led to death only a few years ago – are now better controlled by new therapies. Even if we cannot cure and eradicate these diseases, their natural history has significantly increased by months and years. Although these new therapeutic strategies represent a remarkable advantage over the previous standards of care, it is impossible to ignore the fact that many more patients are now facing the nutritional and metabolic consequences of prolonged immunological and hormonal challenges due to both the illness process itself and the aggressive therapies.”


“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.”
Su KP. Biological mechanism of antidepressant effect of omega-3 fatty acids: How does fish oil act as a 'mind-body interface'? *Neurosignals*, Vol. 17, pp. 144-152, 2009

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

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Prevalence in IFN-α therapy, %</th>
<th>Prevalence in MDD, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/asthenia</td>
<td>39–90</td>
<td>73</td>
</tr>
<tr>
<td>Headache</td>
<td>27–67</td>
<td>33⁶</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>50⁴–¹</td>
<td>34–47⁷</td>
</tr>
<tr>
<td>Psychomotor slowing</td>
<td>40⁸</td>
<td>59–65⁵</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20–39⁶</td>
<td>63</td>
</tr>
<tr>
<td>Irritability</td>
<td>35⁸</td>
<td>50</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9–36</td>
<td>31⁴</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>26–32</td>
<td>62–80²</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15–20</td>
<td>21⁶</td>
</tr>
<tr>
<td>Anorexia</td>
<td>13–19</td>
<td>40</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13–18³</td>
<td>57</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>14⁸</td>
<td>51</td>
</tr>
</tbody>
</table>

¹ [46], unless otherwise specified; ² [99], unless otherwise specified; ³ [100], ⁴ [101]; ⁵ [102]; ⁶ [103]; ⁷ [104].

¹ Nausea, vomiting, bowel problems
² Result from depressed inpatient population.
Organic acids
Fatty acid metabolism: Carnitine
Fatty acid metabolism: Basic information

- “Fatty acid metabolism by mitochondrial β-oxidation is the dominant energy-yielding pathway in most tissues.”
- “Both β- and ω-oxidation systems are contained in peroxisomes.”
- “When the mitochondrial system fails to meet demands, peroxisomes can take over to a limited degree, but lack of the double membrane containment of the mitochondrial means the system is less efficient because substrates may escape and be lost as renal secretory products.”

Adipate and suberate

- “Adipate (adipic acid) and suberate (suberic acid) are six- and eight-carbon-long dicarboxylic acids, respectively.”
- “Low carnitine availability or impaired enzyme activity can slow fatty acid oxidation by decreasing the transport of fatty acids into the mitochondria…”
- “Need for extra carnitine may be indicated when urinary levels of adipate and suberate are elevated.”
Adipate and suberate

• “Carnitine can be synthesized from the essential amino acid, L-lysine.”
• “However, limitations of available lysine due to dietary deficiency or digestive impairment or genetic polymorphism of the required enzymes can cause carnitine requirements to exceed biosynthetic capacity.”
• “Therefore, carnitine is a conditionally essential dietary component.”

Carnitine and Stress

“Loss of carnitine in muscles can result from chronic overuse of lipids by the mitochondria.”

“The regulation of carnitine dependent transfer of fatty acids seems to depend mainly on the rate-limiting activity of carnitine palmitoyltransferase I (CPT-I) and its regulation by malonyl-CoA.”


“The muscle isoform of CPT I is highly sensitive to allosteric inhibition by malonyl CoA, the precursor of fatty acid synthesis.”

Carnitine and Hyperinsulinemia

“It is tempting to speculate that in the preobese state a higher than normal content of malonyl-CoA in liver and muscle, possibly caused by hyperinsulinemia, predisposes to a reduced capacity for fatty acid oxidation and accumulation of fatty acyl-CoA.”


Carnitine and Hyperinsulinemia

Stress accompanied by obesity lessens the positive impact of carnitine in two ways:

1. Higher levels of gluconeogenesis during stress increases lipolysis, causing depletion of endogenous carnitine stores.
2. Obesity and hyperinsulinemia increases levels of the fatty acid precursor malonyl CoA, which inhibits CPT-I, without which carnitine cannot function.
Adipate and suberate

- “A secondary cause of elevated adipate and suberate is riboflavin insufficiency.”
- Once they are inside the mitochondria, fatty acids cannot undergo oxidative metabolism without riboflavin coenzymes.”

Ethylmalonate

- “Ethylmalonate accumulation is traced to different pathways than the long-chain fatty acid oxidation origins of adipate and suberate.”
- “Although the exact origin is somewhat unclear, current evidence suggests that ethylmalonate is formed from butyrate.”
- “Patients with ethylmalonic aciduria also have elevated levels of butyryl-CoA (and isobutyryl-CoA from isoleucine catabolism).”
Using the Organic Acids Test – Part 3
Dr. Jeff Moss

Ethylmalonate

• “Circulating butyrate, a short-chain fatty acid with four carbons, may be derived from intestinal bacterial metabolism.”
• “Butyryl-CoA is normally carried by carnitine into oxidative pathways.”
• “Just as for the long-chain fatty acids, carnitine may be insufficient to clear butyrate or riboflavin may be insufficient to sustain FAD, causing slowing of the rate of oxidation.”
• “Under these conditions, free butyrate is available for other reactions, including carboxylation to form ethylmalonate.”

Ethylmalonate

• “Thus, urinary ethylmalonate elevation shares carnitine and riboflavin dependencies with adipate and suberate, but the precursor arises from different metabolic sources.”
• “This may explain why in evaluating large numbers of organic acid profiles some individuals have elevated adipate and suberate with normal ethylmalonate, whereas other show the opposite pattern.”
Ethylmalonate

• “Patients with ethylmalonic acidurias should not be treated with medium-chain triglycerides that produce metabolic stress from the accumulation of medium fatty acyl-carnitines.”
• “Glycine (250 mg/kg/d) has been found to be a useful adjunct in addition to carnitine and vitamin B₂ in the treatment of these patients.”

Ethylmalonate

• “Ethylmalonate excretion may also be stimulated by isoleucine loading, indicating that it may be an intermediate produced in the isoleucine catabolic pathway.”
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### Diagram

- **Hepatocyte**
  - Intestinal Bacteria
  - Butyrate
  - Ethylmalonate
  - Carnitine Shuttle
  - ATP
  - CO₂ + H₂O
  - Fatty Acids
  - PEROXOSOMES
  - Mitochondria
  - Receptors
  - Lipoprotein

### Considerations for the Catabolic Patient

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<tr>
<th>Signs &amp; Symptoms</th>
<th>Consideration</th>
<th>Treatment Plan</th>
<th>Monitor</th>
<th>Supplementation</th>
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</thead>
<tbody>
<tr>
<td>Optimize pH</td>
<td>Optimize fluid and electrolyte balance</td>
<td>Morning arterial pH/urine pH</td>
<td></td>
<td>Potassium Citrate, L-Ornithine (Moss)</td>
</tr>
<tr>
<td>Optimize muscle mass (reduce sarcopenia)</td>
<td>Pay special attention to protein and amino acids</td>
<td>Body composition: Skinfold thickness, grip strength, knee extension</td>
<td></td>
<td>Amino acids: Casein, Pea Protein, Soy Protein</td>
</tr>
<tr>
<td>Reducing inflammation</td>
<td>Reduce inflammation</td>
<td>Inflammatory biomarkers: CRP, ESR, ferritin, CRPP</td>
<td></td>
<td>Anti-inflammatory agents: DMSO, NAC, NLS, COX-2 inhibitors, TNF-α</td>
</tr>
<tr>
<td>Improving insulin sensitivity</td>
<td>Watch carbohydrate/protein ratio</td>
<td>Fasting glucose, Fasting insulin, Cravings</td>
<td></td>
<td>Metabolic Synergy (DFS), Polypeptide</td>
</tr>
<tr>
<td>Optimize dietary carbohydrate/protein ratio</td>
<td>Right food choices, reduce carbohydrate intake</td>
<td>Diet plan: Optimal protein intake = 1.0 - 1.2 g/kg body weight</td>
<td></td>
<td>Protein supplements: Polypeptide, DFS</td>
</tr>
<tr>
<td>Optimize GI function</td>
<td>Dietary changes, supplementation of digestive aids</td>
<td>Patient signs and symptoms: Bloating, Nausea, abdominal pain, diarrhea</td>
<td></td>
<td>Multi-Vitamin (Vital Nutrients)</td>
</tr>
<tr>
<td>Optimize micronutrient deficiencies/indiscomes</td>
<td>Supplementation of multi vitamins, D, Iodine, and Zinc</td>
<td>Serum 25-OH vitamin D, Fatigue scores, Erythrocyte sedimentation, Zinc test</td>
<td></td>
<td>Multi-Vitamin (Vital Nutrients)</td>
</tr>
</tbody>
</table>

**Presented by:**

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Thank you!!