Metabolomics in nutrition research: biomarkers predicting mortality in children with severe acute malnutrition

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Objectives

• Comprehensive profile of metabolic status at presentation (tandem MS, centralized microassays)

• Characterize changes in >100 FA, AA metabolites, hormones, growth factors, cytokines during nutritional recovery

Hypothesis: hormonal and metabolic factors at baseline predict mortality during treatment.
Patients | n | %
--- | --- | ---
Age | 16.3 ± 8.9 (range 6 mo – 5 yr) | 
Males | 43/75 | 57
HIV+ | 18/75 | 24
Malaria | 7/74 | 10
Edema | 42/75 | 57
Wt z | -4.8 ± 1.5 | 
Length z | -3.2 ± 1.5 | 
Wt/Ht z | -4.2 ± 1.4 | 
Mortality | 9/74 | 12.2

Bartz S, Mody A et al. J Clin Endo Metab in press
BLOOD SAMPLES

F 75
F 100
RUTF

Micronutrients

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Leptin, adiponectin, and ghrelin in malnutrition

**Consequences**

- ↓ energy expenditure
- ↑ food intake
- ↓ insulin sensitivity (glucose sparing)
- ↑ food intake
- ↑ GH
Metabolic response to malnutrition

Lipolysis
Depletion of fat reserves

Glycerol
NEFA

FAO
HGP
Fatty liver
IGF-1

Reduced bone growth
↓ IGF-1
↑ cortisol

FAO
↓ Glucose uptake / oxidation
↓ Protein synthesis
↓ Proteolysis (esp. if edema)
Hypoaminoacidemia
↓ Amino acid utilization
Metabolic response to malnutrition
Metabolic recovery from malnutrition

Lipogenesis
Repletion of fat stores

↑ Bone growth

↑ Glycogen
↓ HGP
↓ ALT
↑ IGF-1

↑ Glucose uptake / oxidation
↑ Protein synthesis
↑ Albumin, AA
↑ Amino acid utilization
**Metabolic recovery from malnutrition**

- Lipogenesis
  - ↑ leptin
  - ↑ adiponectin

- Ghrelin
  - ↓ Ghrelin
  - ↓ GH

- Insulin
- Cortisol
- Adiponectin

- Glu uptake / oxidation
- Protein synthesis
- Albumin, AA
- Amino acid utilization

- Bone growth
- GH induction of IGF-1

- HGP
- ALT
- IGF-1
Baseline factors associated with mortality
(univariate analysis)

<table>
<thead>
<tr>
<th>Factor</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight z</td>
<td>&lt; 0.02</td>
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<tr>
<td>MUAC</td>
<td>&lt; 0.002</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>&lt; 0.02</td>
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<tr>
<td>PYY</td>
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</tr>
<tr>
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<td>&lt; 0.01</td>
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<td>TNFα</td>
<td>&lt; 0.02</td>
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<tr>
<td>Malaria, Edema, Ketones, NEFA</td>
<td>NS</td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
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<tr>
<td>Phosphorus</td>
<td></td>
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<td>CRP</td>
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Bartz S, Mody A et al.  J Clin Endo Metab in press
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<td>Leptin</td>
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Bartz S, Mody A et al. J Clin Endo Metab in press
Adapted from Bartz S, Mody A et al. J Clin Endo Metab in press
Multivariate logistic regression analysis.

OR refers to Odds Ratio for mortality.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>OR</th>
<th>p-value</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Wt/Ht z score</td>
<td>0.546</td>
<td>0.214</td>
<td>0.211-1.417</td>
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<tr>
<td>HIV status</td>
<td>116.84</td>
<td>0.022</td>
<td>2.005-6809.128</td>
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<tr>
<td></td>
<td>5</td>
<td></td>
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</tr>
<tr>
<td>Leptin</td>
<td>0.906</td>
<td>0.035</td>
<td>0.827-0.993</td>
</tr>
<tr>
<td>HMW Adiponectin</td>
<td>1.000</td>
<td>0.184</td>
<td>0.999-1.001</td>
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Bartz S, Mody A et al.  J Clin Endo Metab in press
**Cord blood hormones and growth factors in SGA infants**

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<tbody>
<tr>
<td>Insulin</td>
<td>↓</td>
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<tr>
<td>IGF-1</td>
<td>↓</td>
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</tr>
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Conclusions

• FAO provides primary energy source for GNG and cardiopulmonary function in children with SAM

• ↓ muscle proteolysis, AA utilization severe malnutrition (unless infected)

• Changes in fatty acid and AA metabolism driven by changes in hormones and growth factors (ghrelin, GH, insulin, cortisol, IGF-1)

• Roles of GI hormones paradoxical and unclear

• Malnourished patients hypoadiponectinemic and insulin-resistant

• Catabolic state reversed in 2 wks of formula feeding

• Major biochemical factor predicting mortality low leptin (but not NEFA or ketones): sustain energy production, immune function
Potential Implications

- Metabolic and hormonal profiling - comprehensive analysis of adaptations to childhood malnutrition and treatment; other disorders

- Leptin marker of adipose reserve - utility as marker of pre-clinical malnutrition

- Leptin as clinical biomarker for mortality in edematous + non-edematous

- Role of leptin in defense vs infection (microbiome)

- Leptin as adjunct to nutritional therapy
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