Why are trace elements important in burns?

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Mette M Berger - **Disclosures**

**Grants:** Baxter, BBraun, Fresenius Kabi
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**Member of ICU Guidelines working groups of ESPEN & ESICM – Chair of the MEN section**
<table>
<thead>
<tr>
<th>Element</th>
<th>Store</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fe</td>
<td>3-5 g</td>
<td>liver, spleen &gt; Hb, myoglobin, cytochromes</td>
</tr>
<tr>
<td>Zn</td>
<td>1.4-2.3 g</td>
<td>bone &gt; genitalia, skin, liver, kidney, muscle, pancreas</td>
</tr>
<tr>
<td>Cu</td>
<td>100 mg</td>
<td>liver, enzymes</td>
</tr>
<tr>
<td>I</td>
<td>20-50 mg</td>
<td>60% thyroid &gt; muscle, ovaries, blood</td>
</tr>
<tr>
<td>Se</td>
<td>6-20 mg</td>
<td>liver, kidney &gt; muscle, bone, blood</td>
</tr>
<tr>
<td>Mn</td>
<td>12-16 mg</td>
<td>mitochondria (liver, bone, kidney, pancreas, small intestine)</td>
</tr>
<tr>
<td>Mo</td>
<td>9-16 mg</td>
<td>mitochondria (same as Mn)</td>
</tr>
<tr>
<td>Cr</td>
<td>4-6 mg</td>
<td>spleen, heart, kidney</td>
</tr>
<tr>
<td>Co</td>
<td>&lt; 1 mg</td>
<td>blood</td>
</tr>
<tr>
<td>F</td>
<td>&lt; 1 mg</td>
<td>bone</td>
</tr>
</tbody>
</table>
Specificities of major burns

• Oxidative stress

• Large open wounds with exudates persisting until wound closures

• Metabolic storm with high nutritional needs
WHY DO MAJOR BURNS SUFFER OXIDATIVE STRESS?
Burns $\rightarrow$ massive production of Free radicals

ROS
Reactive Oxygen Species
Trace elements with antioxidant function

- Superoxide anion ($O_2^-$)
- Hydrogen peroxide ($H_2O_2$)
- Hydroxyl radical ($OH^-$)
- SOD (CuZn, Mn)
- GPX (Se)
- Catalase (Fe, Cu)

Lipid peroxidation
Oxidative stress in major thermal burns: Its implications and significance
Babu & Babu, Indian J Burns, 2018;26:38

30 patients from January 2016 to December 2016
Inclusion hospitalization within 24 h of burn, burn surface 20%–50%
Oxidative stress in major thermal burns: Its implications and significance
Babu & Babu, Indian J Burns, 2018;26:38

Total antioxidant capacity (TAC) replaces the separate measure of antioxidant molecules (not practical & their antioxidant effects are additive)
Effects of severe thermal injury on the zinc concentrations both in the serum and in the liver. mean±sem, \( n=5 \). * \( P<0.001 \), ** \( P<0.01 \) and # \( P<0.05 \) vs. the corresponding normal control
Wound healing requirements

Perfusion

Nutrients:
- amino acids
  Gln, Arg, Cys
- Glucose
- FFA

Micronutrients:
- Vitamins
- Trace elements

Singh, JYI 19, 2008
Trace element roles in wound healing

Copper: Collagen and elastin synthesis, Immune function

Iron: Wound healing, oxygen transport, Immune function

Selenium: AOX, Immune function

Zinc: All anabolic pathways (protein synthesis), AOX, Immune function
After injury wounded tissue must establish haemostasis via coagulation and clot formation. Injury is followed by immune infiltration and inflammation, thus preventing infection and allowing room for granulation. Fibroblast, epithelial cells, keratinocytes and endothelial cells, will proliferate and migrate into wounds to deposit ECM and re-populate the injury site → wound closure. Finally, matrix deposition and clearance regulates the development of scar formation.
Collagen & Elastin synthesis – Copper dependent

Hydroxylation

Prolyl-hydroxylase
Lysyl-hydroxylase

O₂
α-ketoglutarate
Ascorbic acid
Fe²⁺

CO₂
Succinate
Fe³⁺

Glycosylation

OH
OH
NH₂

Assembly of 3 pro-α chain
Procollagen triple helix formation

Lysyl oxidase (a copper-containing enzyme)

Lysine Residues of collagen and elastin to allysin.
### Trace element deficiencies in major burns – known since 1967

<table>
<thead>
<tr>
<th>SUMMARY OF FINDINGS</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Zn deficiency persisting for 2-3 months</td>
<td>Pories et al 1967</td>
</tr>
<tr>
<td>Low Zn skin concentration in the burned area</td>
<td>Henzel et al 1970</td>
</tr>
<tr>
<td>In children, low Zn cutaneous levels and high Zn levels in exudates</td>
<td>Larson et al 1970</td>
</tr>
<tr>
<td>Large urinary zinc losses</td>
<td>Fell et al 1973</td>
</tr>
<tr>
<td>Low plasma copper and zinc concentrations: with late normalisation</td>
<td>Lafargue et al 1976</td>
</tr>
<tr>
<td>Cu and Zn deficiency</td>
<td>Sanchez-Agreda et al 1978</td>
</tr>
<tr>
<td>Cu and Zn deficiency in children not corrected by enteral supplements</td>
<td>Pochon et Klöti 1979-1981</td>
</tr>
<tr>
<td>Large urinary zinc losses</td>
<td>Shakespeare 1982</td>
</tr>
<tr>
<td>Low Se plasma levels with low GSHPx activity</td>
<td>Hunt et al 1984</td>
</tr>
<tr>
<td>Low plasma Cu and Zn concentrations with alterations of carrier proteins</td>
<td>Shewmake et al 1988</td>
</tr>
<tr>
<td>Persistent alterations of Cu, Se, Zn</td>
<td>Boosalis et al 1986-1991</td>
</tr>
<tr>
<td>Large cutaneous Cu, Se and Zn losses with negative balances</td>
<td>Berger et al 1992</td>
</tr>
<tr>
<td>Low Zn concentrations in wounds, with low plasma concentrations</td>
<td>Selmanpakoglu et al 1994</td>
</tr>
<tr>
<td>Copper deficiency in burned children,</td>
<td>Cunningham et al 1991-96</td>
</tr>
<tr>
<td>Fatal cardiac arrhythmia due to copper deficiency</td>
<td>Sampson et al 1996</td>
</tr>
</tbody>
</table>
WHY ARE THE NEEDS INCREASED?

- NEEDS ↑ (AOX, TISSUE REPAIR)
- LOSSES ↑
Burns – trace element balances from Day 1 to 7

In:  all iv fluids
    blood products
    micronutrient supplements
    enteral feeds

Out: urine
     feces
     aspirations: bronchial, gastric
     drains
     cutaneous exudates
     blood losses during surgery

TE precautions
- Gloves
- Collection bags
Burn TE balance study 1987-1988
TE extraction method

15,000 l d’eau bi-distillée
Burns: Trace element losses


Days after injury

- **Cu (mg)**
  - **Urine**
  - **Feces**
  - **Aspirations**
  - **Cutaneous exsudate**

- **Zn (mg)**
  - **Urine**
  - **Feces**
  - **Aspirations**
  - **Cutaneous exsudate**

- **Se (µg)**
  - **Urine**
  - **Feces**
  - **Aspirations**
  - **Cutaneous exsudate**

N=10, 33% BSA
Impaired Zn and Cu status in children with burn injuries
Voruganti VS et al, Burns 2006, 31: 711

<table>
<thead>
<tr>
<th>Child</th>
<th>Zinc</th>
<th>Copper</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma (mg/l)</td>
<td>Urine (mg/d)</td>
</tr>
<tr>
<td>1</td>
<td>Admission</td>
<td>Discharge</td>
</tr>
<tr>
<td>2</td>
<td>0.69</td>
<td>0.65</td>
</tr>
<tr>
<td>3</td>
<td>0.60</td>
<td>0.77</td>
</tr>
<tr>
<td>4</td>
<td>0.53</td>
<td>0.52</td>
</tr>
<tr>
<td>5</td>
<td>0.84</td>
<td>0.70</td>
</tr>
<tr>
<td>6</td>
<td>0.59</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Mean ± S.D. Zinc: 0.61 ± 0.15, 0.66 ± 0.15; Cu: 0.36 ± 0.21, 0.44 ± 0.20

Six children burned 54 ± 9% TBSA, age 10.2 ± 2.3 years, weight 29.3 ± 7.5 kg
Dietary Zn and Cu intakes were 3 times the dietary reference
TE after major burns increase [burned skin] and modulate local protein metabolism

Trace element trials

- Animal
- Human
TE and infections after major burns
The 3 CHUV trials

• Design: 2 consecutive prospective randomised placebo controlled supplementation trials
• (+ 1 preliminary open trial)
• Intervention: Cu, Se, Zn IV (group TE) or vehicle (group V) for 8 or 14-21 days
• Complications collected over 30 days
• Number of infections, timing, location and antibiotherapy recorded
• Pneumonia: early (<48 hrs) and nosocomial counted separately
Burns repletion trials 2-3
Supplements and investigations

<table>
<thead>
<tr>
<th></th>
<th>Group TE</th>
<th>Group Vehicle</th>
<th>Mean daily TE content of feeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>3.75 mg</td>
<td>Ø</td>
<td>2.7 ±0.7 mg</td>
</tr>
<tr>
<td></td>
<td>(59 μmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td>375 μg</td>
<td>Ø</td>
<td>90 ±24 mg</td>
</tr>
<tr>
<td></td>
<td>(4.8 μmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>37.5 mg</td>
<td>Ø</td>
<td>21.5 ±5.6 mg</td>
</tr>
<tr>
<td></td>
<td>(574 μmol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glu-1-P</td>
<td>12.5 mmol</td>
<td>Ø</td>
<td>-</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>ICU Days</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
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<tbody>
<tr>
<td>Blood</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Urine</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Calorimetry</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Trace element supplementation after major burns modulates antioxidant status and clinical course by way of increased tissue trace element concentrations\textsuperscript{1–3}

Mette M Berger, Malcolm Baines, Wassim Raffoul, Messod Benathan, René L Chiolero, Chris Reeves, Jean-Pierre Revelly, Marie-Christine Cayeux, Isabelle Sénéchaud, and Alan Shenkin

**Mean plasma TE over time**

![Graphs showing mean plasma TE over time for Copper, Zinc, Selenium, and plasma GSHPx over days post-injury.](image)

*Am J Clin Nutr 2007; 85: 1293*
Antioxidants in major burns

Accelerated MDA decay with trace elements

Berger & Chiolero, Burns, 21: 507, 1995

Design: PCT
11 patients (5 / 6)
BSA 42 / 43 %
Group control: ø
Group TE: Cu, Se, Zn
Urine: 24 hr coll.

p<0.03
TE repletion trial in major burns: RCT


Days post-injury

Interleukin-6

p < 0.05

n = 20 

mean ± sd 

ref.value < 3
Trace element (Cu, Se, Zn) repletion in Burns - Nosocomial pneumonia

Aggregation of 2 consecutive Randomized Trials → IV
- Cu 3 mg
- Se 300 mcg
- Zn 30 mg

Log Rank
p=0.0014
Wilcoxon
p=0.0019

65% reduction of pneumonia risk
Length of stay: PRCT TE/placebo

Berger et al, Crit Care 2006, 10:R143

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi2</th>
<th>DF</th>
<th>Prob&gt;Chi2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>0.4406</td>
<td>1</td>
<td>0.5068</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>2.4457</td>
<td>1</td>
<td>0.1179</td>
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</table>

Tests Between Groups

<table>
<thead>
<tr>
<th>Test</th>
<th>Chi2</th>
<th>DF</th>
<th>Prob&gt;Chi2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-Rank</td>
<td>5.3770</td>
<td>1</td>
<td>0.0204</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>5.5177</td>
<td>1</td>
<td>0.0188</td>
</tr>
</tbody>
</table>

Probability

Length of ICU stay (days)

37 vs 44 d

LICU/%BSA

n = 41
Burns 46% BSA

0.70 vs 1.02 d/ %BSA
TE after major burns increase [burned skin] and modulate local protein metabolism

*Berger et al, Amer J Clin Nutr, 2007*

<table>
<thead>
<tr>
<th></th>
<th>Group V</th>
<th>Group TE</th>
<th>Group V isotopes</th>
<th>Group TE isotopes</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N isotope / all</td>
<td>10</td>
<td>11</td>
<td>5 / 10</td>
<td>5 / 11</td>
<td></td>
</tr>
<tr>
<td>Patients biopsies (n)</td>
<td></td>
<td></td>
<td>7 / 10</td>
<td>5 / 11</td>
<td>ns</td>
</tr>
<tr>
<td>Sex</td>
<td>4 F / 6 M</td>
<td>2 F / 9 M</td>
<td>3 F / 2 M</td>
<td>1 F / 4 M</td>
<td>ns</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>38 ±16</td>
<td>46 ±15</td>
<td>32 ±9 [26]</td>
<td>46 ±19 [51]</td>
<td>0.22 ns</td>
</tr>
<tr>
<td>Burned BSA (%)</td>
<td>44 ±20 [41]</td>
<td>45 ±22 [40]</td>
<td>45 ±26 [36]</td>
<td>62 ±21 [65]</td>
<td>0.26 ns</td>
</tr>
<tr>
<td>Surgical BSA (%)</td>
<td>34 ±16 [29]</td>
<td>31 ±30 [22]</td>
<td>38 ±19 [30]</td>
<td>56 ±24 [60]</td>
<td>0.29 ns</td>
</tr>
</tbody>
</table>

Data as mean ±SD or [median]. Abbreviations: V = vehicle, TE = Trace elements.

*p = 0.03
Trace element intakes should be revisited in burn nutrition protocols: A cohort study
Jafari P et al, Clin Nutr, 2018;37:958

15 adult patients burned 29 ± 20% BSA for 8 days after injury.
Trace element repletion following severe burn injury: A dose-finding cohort study
Pantet et al, Clin Nutr 2019:18:246  N=139

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period 1 (99–01)</th>
<th>Period 2 (02–05)</th>
<th>Period 3 (06–10)</th>
<th>Period 4 (11–15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific burn IV trace element preparation</td>
<td>1 Specific burn TE-flex®&lt;sup&gt;a&lt;/sup&gt; 5 days/20–30% BSA 10 days/30–40% BSA 21 days/&gt;40% BSA</td>
<td>1 Specific burn TE-flex®&lt;sup&gt;a&lt;/sup&gt; 5 days/20–30% BSA 10 days/30–40% BSA 21 days/&gt;40% BSA</td>
<td>1 Specific burn TE-flex®&lt;sup&gt;a&lt;/sup&gt; 5 days/20–30% BSA 14 days/30–60% BSA 30 days/&gt;60% BSA</td>
<td></td>
</tr>
<tr>
<td>Standard ICU IV micronutrient</td>
<td>None</td>
<td>Stress profile 1&lt;sup&gt;c&lt;/sup&gt; Copper 5.05 mg Selenium 507 μg Zinc 54 mg</td>
<td>Stress profile 2&lt;sup&gt;d&lt;/sup&gt; Copper 4.23 mg Selenium 545 μg Zinc 52.5 mg</td>
<td>Additional 300 μg Se, 20 mg Zn contained in Intestamin&lt;sup&gt;e&lt;/sup&gt; Copper 4.23 mg Selenium 845 μg Zinc 72.5 mg</td>
</tr>
<tr>
<td>Max total daily intravenous TE’s intake</td>
<td>Copper 3.75 mg</td>
<td>Copper 5.05 mg</td>
<td>Copper 4.23 mg</td>
<td>Copper 4.23 mg</td>
</tr>
<tr>
<td>Max total daily intravenous and enteral TE’s intake</td>
<td>No additional enteral intake except minor quantities in enteral feeds</td>
<td>Selenium 375 μg</td>
<td>Selenium 507 μg</td>
<td>Selenium 845 μg</td>
</tr>
</tbody>
</table>

**A** TBSA <40% vs. TBSA ≥40% Cu Plasma

**B** TBSA <40% vs. TBSA ≥40% Se Plasma

**C** TBSA <40% vs. TBSA ≥40% Zn Plasma

**Cu Intake** vs. **Se Intake** vs. **Zn Intake**

[Diagrams and box plots showing copper (Cu), selenium (Se), and zinc (Zn) levels and intakes across different periods and burn severity categories.]
Micronutrients
Replet or supplement?
2 different aims

Statut normal
Loss Insufficient Intake
Deficit
Replete

Toxicity ?
Supplement

+ +++
Parenteral combined trace element supplementation and length of stay (days).

Parenteral combined trace element supplementation and infectious episodes.
| Indication | Nutritional therapy should be initiated early within 12 hours of injury, preferentially by the enteral route. | strong | B |
| Route | We recommend to give priority to the enteral route, parenteral administration being rarely indicated | strong | C |
| Energy requirements & Equations | We recommend considering indirect calorimetry as a gold standard to assess energy requirements. If not available or not suitable, we recommend using the Toronto equation for burn adults. For burn children, we suggest to use Schofield formula | weak | D |
| Proteins | Protein requirements, are higher than in other categories of patients, and should be set around 1.5 to 2.0 g/kg in adults and 1.5 to 3 g/kg/day in children. We strongly suggest to consider glutamine supplementation (or ornithine alpha-keto-glutarate) but not arginine supplementation | strong | D |
| Glucose and glycemia control | We strongly suggest to limit carbohydrate delivery (prescribed for nutritional and drug dilution purpose to 60% of total energy intake, and not to exceed 5 mg/kg/min in both adults and children. We strongly suggest to keep glucose levels under 8 mmol/l (and > 4.5 mmol/l), using continuous intravenous infusion of insulin | strong | E |
| Lipids | We suggest to monitor total fat delivery, and to keep energy from fat <35% of total energy intake | weak | B |
| Micronutrients | We strongly suggest associating, in adults as in children, a substitution of zinc, copper and selenium, as well as of vitamin B1, C, D and E. | strong | C |
| Metabolic modulation | We strongly recommend using non nutritional strategies to attenuate hypermetabolism and hypercatabolism in both adults and children (warm ambient temperature, early excision surgery, non selective beta-blockers, oxandrolone). Unlike adults, we recommend to administer rhGH to burn children with TBSA >60% | strong | B |
Why Trace Elements in Burns

Conclusions

Oxidative stress is massive and requires TE
Acute TE deficiencies ← skin losses
Hypermetabolism → increased requirements
Repletion doses → Restore TE status
   Restore AOX defences
Repletion → clinical benefits:
   Better graft take – less surgery
   ↓ infections, nosocomial pneumonia,
   ↓ length ICU & hospital stay

Burns = a condition with high repletion and elevated nutritional requirements
Thank you