Discovery of human zinc deficiency and its impact 50 years later

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Department of Oncology

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School of Medicine

November, 2011
Zinc Deficiency in Microorganisms, Plants and Animals

1. RAULIN in 1869 - Aspergillus niger
2. SOMMER and LIPMAN in 1926 - Higher Plant Life
3. TODD, ELVEHJEM & HART in 1934 - Rats
4. TUCKER and SALMON in 1955 - Pigs
5. O’DELL and SAVAGE in 1958 - Poultry
6. Prasad et al in 1963 - Man
THE
AMERICAN JOURNAL
OF MEDICINE

Volume 31, 1961
Pages 532-546

Syndrome of Iron Deficiency Anemia,
Hepatosplenomegaly, Hypogonadism, Dwarfism
and Geophagia

ANANDA S. PRASAD, M.D., JAMES A. HALSTED, M.D. and
MANUCHER NADIMI, M.D.
Shiraz, Iran
Zinc-Deficient Farm Boy
Clinical and experimental

Zinc metabolism in patients with the
syndrome of iron deficiency anemia, hepatosplenomegaly,
dwarfism, and hypogonadism

ANANDA S. PRASAD, AUGUST MIALE, JR., Z. FARID, H. H.
SANDSTEAD, and ARTHUR R. SCHULERT Cairo, U. A. R.
CLINICAL MANIFESTATIONS IN ZINC DEFICIENT DWARFS

1. Growth Retardation
2. Hypogonadism in Males
3. Rough Skin
4. Poor Appetite
5. Mental Lethargy
6. Intercurrent Infections
Estimated Percentage of Population at Risk of Zinc Deficiency

Prevalence of ZINC DEFICIENCY

Nearly two billion subjects in the developing world have nutritional deficiency of zinc. In the developing world, the diet consists of mainly cereal proteins with high phytate content which complexes zinc and decreases its availability.

Conditioned deficiency of zinc is also widely prevalent throughout the world. Zinc deficiency has been reported in patients with liver disease, chronic alcoholism, malabsorption syndrome, chronic renal disease, and other chronic diseases including malignancy.
Patient With Severe Zinc Deficiency

- Alopecia
- Orbital and perioral acanthosis
Photograph of Patient After Zinc Therapy
“Mild” Deficiency of Zinc

**Manifestations:**
- Neuro-sensory changes
- Decreased serum testosterone
- Oligospermia
- Hyperammonemia
- Anergy
- Decreased NK activity
- Decreased production of IL-2
- Decreased thymulin activity
- Impaired cognitive functions

**Observed in:**
- Experimental human model studies.
- Elderly
- Pre-menopausal women
Therapeutic Impact of the Discovery of Essentiality of Zinc in Human

1. In infants and children in developing countries with acute diarrhea and respiratory tract infections

2. Wilson’s Disease

3. Common Cold

4. Sickle Cell Disease

5. Prevention of blindness due to age related macular degeneration (AMD)

6. Acyzol for Co poisoning (*Russian Study*)

7. Decreased incidence of infections in the elderly
Evidence that Zinc Acetate Lozenges are Effective for Treatment of Cold Duration and Cold Symptoms

### Duration (Days) of Symptoms of the Common Cold

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zinc Supplemented Group (n=25)</th>
<th>Placebo Supplemented Group (n=25)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Symptoms</td>
<td>$4.00\pm1.04^a$</td>
<td>$7.12\pm1.26$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td></td>
<td>(3.57 to 4.42)$^b$</td>
<td>(6.59 to 7.64)</td>
<td></td>
</tr>
<tr>
<td>Specific Symptoms:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore Throat</td>
<td>$1.96\pm1.83$</td>
<td>$3.24\pm2.93$</td>
<td>0.07</td>
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<tr>
<td></td>
<td>(1.2 to 2.71)</td>
<td>(2.02 to 4.45)</td>
<td></td>
</tr>
<tr>
<td>Nasal Discharge</td>
<td>$3.00\pm1.63$</td>
<td>$4.56\pm3.01$</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(2.32 to 3.67)</td>
<td>(3.31 to 5.80)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>$2.16\pm1.70$</td>
<td>$5.08\pm2.97$</td>
<td>$&lt;0.0001$</td>
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<tr>
<td></td>
<td>(1.45 to 2.86)</td>
<td>(3.85 to 6.30)</td>
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<tr>
<td>Hoarseness</td>
<td>$1.00\pm1.44$</td>
<td>$2.20\pm2.90$</td>
<td>0.07</td>
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<tr>
<td></td>
<td>(0.40 to 1.59)</td>
<td>(1.00 to 3.39)</td>
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</tr>
<tr>
<td>Muscle Ache</td>
<td>$0.80\pm1.22$</td>
<td>$2.00\pm2.25$</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>(0.29 to 1.30)</td>
<td>(1.06 to 2.93)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>$0.52\pm1.35$</td>
<td>$1.12\pm2.00$</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>(0.04 to 1.05)</td>
<td>(0.29 to 1.94)</td>
<td></td>
</tr>
</tbody>
</table>
Group Mean Symptom Scores Logged During Treatment

Day of Cold

Placebo

Zinc

Mean

S.E.M.

p = 0.0002
Zinc treatment was significantly effective in reducing plasma levels of sICAM-1.

Plasma sICAM-1 and ICAM-1 on the cell surfaces function as receptors for the HRV14 rhinovirus. Decreased presence of this “rhinovirus docking” receptor lessens the opportunity for rhinovirus attachment to cells.
Effect of zinc and placebo supplementation on incidence of infection in elderly subjects after 12M of supplementation

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zinc supplementation</th>
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<tbody>
<tr>
<td>n=25</td>
<td>n=24</td>
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<tr>
<td>P=0.001</td>
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</table>

%
Effect of zinc supplementation on plasma hsCRP in elderly after 6M of supplementation

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zinc Suppl</th>
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<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td></td>
<td>n=20</td>
<td>20</td>
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</tbody>
</table>

\[P=0.001\]
Effect of zinc supplementation on plasma MDA+HAE in elderly after 6M of supplementation

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zinc Suppl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=20</td>
<td></td>
<td>n=20</td>
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</tbody>
</table>

MDA+HAE, μM

P=0.001
Effect of zinc supplementation on IL-2 mRNA in PMNC isolated from elderly after 6M of supplementation

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Zinc Suppl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2 mRNA/18S RNA</td>
<td>0.40 ± 0.02</td>
<td>0.60 ± 0.04</td>
</tr>
</tbody>
</table>

P = 0.001
Zinc

Anti-apoptotic molecules (BCL2, BCLXL, cIAP-2)

Growth Factors (VEGF, cyclin D1, EGFR, etc)

Cytokines (IL-1β, IL-6, IL-8, TNF-α, MCP-1)

Enzymes (iNOS, COX2)

Adhesion molecules (Integrins, ICAM-1, VCAM-1, E-selectin)

Fibrinogens

NIK

IKK

NF-κB activation

TRAF pathway

oxLDL

ROS

SOD, MT

NADPH OXIDASE

A20

PPAR-α, -γ

ROS

NF-κB activation

Cell Growth

Inflammation

Coagulation

Atherosclerosis
Collaborators

Bin Bao          Doh-Yeel Lee
Frances Beck     Sudesh Mahajan
George Brewer    Sheila Meftah
Mireille Dardenne Donald Oberleas
James Halsted    Parviz Rabbani
Joseph Kaplan    Harold Sandstead
Omer Kucuk       Fazlul Sarkar
Thank You for Your Attention!