ZINC SUPPLEMENTATION IN LIVER DISEASE

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ZINC – ESSENTIAL MINERAL

Functions:

- Hemoglobin
- Immune function
- Molecules and enzymes
- Antioxidant
- Appetite, growth, development
ANTIOXIDANT

Copper

Zinc

Superoxide Dismutase (SOD)

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Adult RDA:

Men – 11mg/day

Women – 8mg/day (more with pregnancy and breastfeeding)

Deficiency is rare = <70ug/dL

UL = 40mg/day
May be supplemented if:

- Strict vegetarian
- >50 years old
- Severe wounds
- Kidney disease
- Digestive/absorptive impairments
- Alcoholism
THE LIVER

Functions:

- Removes toxins and waste
- Produces bile
- Stores glycogen
- Produces proteins
LIVER FUNCTION

- **Hepatic artery** - takes blood from the heart
- **Portal vein** - brings blood from the bowel
- **Storage**
- **Right lobe**
- **Left lobe**

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CHRONIC LIVER DISEASE (CLD)

Infections:
- Hepatitis A
- Hepatitis B
- Hepatitis C

Cancer

Alcohol Abuse

NAFLD

Autoimmune

Genetic Disorders

Medications and Drugs
PROCESS OF CIRRHOSIS AND LIVER FAILURE

1. Chronic inflammation
2. Scar tissue (fibrosis)
3. Reduced blood flow
4. Severe scaring (cirrhosis)
5. Liver Failure
STUDY 1:

Serum zinc value in patients with hepatitis virus-related chronic liver disease: association with the histological degree of liver fibrosis and with the severity of varices in compensated cirrhosis.


*Journal of Clinical Biochemistry and Nutrition.* 2014
STUDY I:

Purpose:

To investigate the association of serum zinc and the severity of liver fibrosis and esophageal varices in HBV and HCV-related chronic liver disease.

Retrospective Cohort
**STUDY 1:**

**Inclusion criteria:**
- Chronic liver disease
- HBV or HCV
- Liver biopsy January 2008 - July 2012

**Exclusion criteria:**
- Blood labs not done with biopsy
- Presence of other liver diseases
- Immunosuppressive therapy
- HIV virus co-infection.

STUDY 1:

Characteristics:
• n=576 (265 males, 311 females)
• Mean age: 61 years
• Japan

Methods:
• Serum zinc (ug/dl)
• Fibrosis stages F0-F4 – Metavir grading

Zinc values in relation to degree of liver fibrosis:

STUDY 1:

Conclusion:
Zinc value is associated with the histological progression of liver fibrosis.

STUDY 1:

Strengths:  
- Fairly large sample size  
- HBV and HCV only  
- Liver biopsy  
- Consistent zinc measurement

Weaknesses:  
- Dietary recall  
- Multivitamin  
- Single time point


Positive (+) Quality Rating
STUDY 2:

Low plasma zinc is associated with higher mitochondrial oxidative stress and faster liver fibrosis development in the Miami adult studies in HIV cohort.

Martinez SS, Campa A, Li Y, et al

*Journal of Nutrition. 2017*
STUDY 2:

Purpose:

To investigate whether **plasma zinc**, an antioxidant, is related to mitochondrial oxidative stress and the progression of **liver fibrosis** in the Miami Adult Studies in HIV (MASH) cohort.

*Prospective Cohort*

STUDY 2:

Inclusion criteria:

- Chronic liver disease
- HIV or HIV+HCV
- 19-60 years old
- BMI >18 and <40

Exclusion criteria:

- Uncontrolled diabetes, heart disease, hyperlipidemia, or metabolic syndrome
- HBV, hepatic encephalopathy, carcinoma or cirrhosis
- Heavy tobacco smokers
- Pregnant

STUDY 2:

Characteristics:

• n=487 (170 females and 317 males)
• Mean age: 47.1 years
• Miami, Florida
• Predominantly African American males
• Mean BMI: 27.4
STUDY 2:

Methods:

• 34 months
• Visits every 3 months
• Fasting blood draw every 6 months with metabolic panel
  • Plasma Zinc
  • Oxidative stress
  • Fibrosis-4 (FIB-4) score
• Models were adjusted for sex, race, BMI, CD4 cell count, HIV viral load, AUDIT, and tobacco use.

STUDY 2:

Conclusion:
Lower plasma zinc is associated with faster progression of liver fibrosis in HIV.
STUDY 2:


Strengths: Positive (+) Quality Rating

• Length of study
• n = 487
• Quantify the relationship between zinc status and fibrosis

Weaknesses:

• Liver biopsy
• Dietary Zinc
• Multivitamin
• Exclusion criteria - Cirrhosis
STUDY 3:

Effects of Low Dose Zinc Supplementation on Biochemical Markers in Non-alcoholic Cirrhosis: A Randomized Clinical Trial.

Hossein Somi M, Rezaeifar P, Ostad Rahimi A, Moshrefi B.

*Archives of Iranian Medicine*. 2012.
STUDY 3:

Purpose:

Evaluate the effects of low dose **zinc supplementation** on biochemical markers and underlying disease status in non-alcoholic **cirrhotic patients**.

*Double-blind, placebo-controlled, randomized clinical trial*
## Inclusion criteria:

- Patients with histologically documented liver cirrhosis

## Exclusion criteria:

- Child-Pugh >12
- Alcoholic cirrhosis
- Hepatocellular carcinoma
- <18 years
- Anabolic hormone, diuretics or albumin use in the last month
- Ascites, peripheral edema, or severe renal or respiratory disorders

STUDY 3:

Characteristics:

- Initial n=60 (39 males, 21 females)
- Final n=52
- 40% HBV infection
- 3.3% HCV infection
- 38.3% autoimmune hepatitis
- 8.3% cryptogenic and other types
- Mean age: 51.3 years
- Tabriz, Iran
**Methods:**

- 34 months
- Visits every 3 months
- Fasting blood draw every 6 months with metabolic panel
- Plasma Zinc
- Oxidative stress (mtDNA 8-oxo-dG)
- Fibrosis-4 (FIB-4)

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**INTERVENTION**

Discontinued intervention due to adverse effects (n = 5) of severe gastrointestinal discomfort, nausea, and vomiting

- Analyzed (n = 25)
  - Excluded from analysis (n = 0)

**PLACEBO**

Lost to follow-up (n = 3) (One patient died from MI, two transferred to another facility and another city.)

Discontinued intervention (n = 0)

- Analyzed (n = 27)
  - Excluded from analysis (n = 0)
Methods:

- 90 days
- 25 subjects received 50mg zinc/day
- 27 subjects received placebo
- Visited monthly
- Assessed on day 1 and day 90 of the trial
  - Child-Pugh score
  - Serum Zn, Cu, Fe
  - Albumin, creatinine, BUN
Effects of Low Dose Zinc Supplementation on Biochemical Markers in Non-alcoholic Cirrhosis: A Randomized Clinical Trial.


Serum Zinc Before and After Intervention

<table>
<thead>
<tr>
<th>Time</th>
<th>Serum Zinc Before Intervention (ug/dL)</th>
<th>Serum Zinc After Intervention (ug/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>63.97</td>
<td>67.42</td>
</tr>
<tr>
<td>Day 90</td>
<td>64.69</td>
<td>77.87</td>
</tr>
</tbody>
</table>

* Significantly different from placebo, p<0.002, P<0.001
Serum Copper Before and After Intervention

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Copper (µg/dL)</td>
<td>Serum Copper (µg/dL)</td>
</tr>
<tr>
<td>136.43</td>
<td>127.37</td>
</tr>
<tr>
<td>135.45</td>
<td>106.42</td>
</tr>
</tbody>
</table>

50mg Zinc vs Placebo

- P = 0.01
- P < 0.0001

Increased liver Cu

Oxidative stress

Increased fibrosis

Cu not excreted in bile
Conclusion:
Low dose Zn supplementation could prevent deterioration of clinical status of cirrhosis and prevent excess Cu accumulation in non-alcoholic cirrhotic patients.

Zn supplementation trends towards improvement in liver function.
STUDY 3:

Strengths: Positive (+) Quality Rating

• Double-blind, placebo-controlled, randomized clinical trial.

Weaknesses:

• Short time frame
• Small sample size
• “Low-dose” Zinc supplement was above the UL for Zinc (long-term effects)
• Quality of life

FURTHER RESEARCH

Take Home Message

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This Photo by https://grist.org/living/what-happens-if-i-flush-leftover-drugs-down-the-toilet.

Key Home Message

- Human studies
- Dietary Zinc
- Long-term effect
- Quality of life

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REFERENCES


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