Nutrition, Aging and a Healthy Immune System

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Talk Outline

• Infections – leading cause of morbidity and mortality in elderly

• Factors that contribute to high incidence, morbidity, and mortality from infections in elderly

• Dietary strategies to improve immune response and resistance to infection in elderly
## Number of People Over the Age of 60

<table>
<thead>
<tr>
<th>Year</th>
<th># &gt; 60 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>600 Million</td>
</tr>
<tr>
<td>2025</td>
<td>1.2 Billion</td>
</tr>
<tr>
<td>2050</td>
<td>2.0 Billion</td>
</tr>
</tbody>
</table>

The World Health Report 2003
Elderly have Higher Incidence of and Morbidity/Mortality from Infectious Diseases

- Pneumonia
- Tuberculosis
- G.I. infections
- HIV/AIDS
- Urinary tract infections
- Herpes zoster
Why Are Elderly More Susceptible to Infectious Diseases?

- Impaired immune response particularly in the T cell-mediated function
- Increased pathogen virulence in aged host
- Genetics
- Changes in gut microflora
- Other physiological changes
↓↑ Antibody prod.
↓ DTH
↑ memory cells
↓ Th1/Th2
↓ proliferation
↓ IL-2
impaired signal transduction

- Infectious diseases
- Autoimmune diseases
- Cancer
- Asthma
Why Are Elderly More Susceptible to Infectious Diseases?

- Impaired immune response particularly in the T cell-mediated function
- Increased pathogen virulence in aged host
- Genetics
- Changes in gut microflora
- Other physiological changes
Numerous CVB3 variants exist

- **Virulent** *(CVB3/20)*

- **Avirulent** *(CVB3/0)*
  - does not normally cause heart damage (myocarditis)

- 99.7% homologous
A Benign Virus Becomes Pathogenic After Passing Through a Se deficient Host

Effect of Host Age on CVB3 Virulence

CVB3/0 → Young

Young → Low Titer

Low Titer → High Titer

High Titer → Old

Dr. Raina Gay
Effect of Host on CVB3 Virulence

Effect of Virus Origin on Heart Titer in Young Mice

*Significantly higher than virus passed from young host at \( p < 0.001 \), mean ± SEM.

Effect of Passage Through an Old Versus Young Host on CVB3/0 Sequence

<table>
<thead>
<tr>
<th>Segment</th>
<th>Nucleotide Number (5’-3’)</th>
<th>CVB3/0 Stock</th>
<th>CVB3/20</th>
</tr>
</thead>
<tbody>
<tr>
<td>E8</td>
<td>234</td>
<td>C</td>
<td>T</td>
</tr>
<tr>
<td>P3</td>
<td>598</td>
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<th>Nucleotide Number (5'-3')</th>
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<tr>
<td>E8</td>
<td>234</td>
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<th>Mice that Received Passed CVB3/0 from Old</th>
</tr>
</thead>
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<tr>
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</tbody>
</table>
Why Are Elderly More Susceptible to Infectious Diseases?

- Impaired immune response particularly
- Increased pathogen virulence in aged host
- Change in gut microflora?
Changes in Gut Microflora With Age

- A limited number of studies has indicated that structural changes occur in the ecosystem in the elderly people. Species such as bifdobacteria, which are regarded as being protective, are thought to decline in numbers and diversity, whereas clostridia and enterobacterial populations, which are viewed as being detrimental to health, increase.

Why Does the Gut Microflora Change with Age?

- Change in mucin composition
- Decline in immune response
- Excessive use of antibiotics
- Dietary changes
- Others
Can we prevent age-associated immune dysfunction and/or viral evolution?

- Malnutrition
- Aging

- Impaired Host Defense
- Increase Pathogen Virulence

Infection
Older Adults Are at an Increased Risk for Deficiency of Several Micronutrients

Vitamin E  Folate
Vitamin A  Zinc
Vitamin C  Selenium
Vitamin B_6
A High Percentage of Older Adults Are Overweight

<table>
<thead>
<tr>
<th></th>
<th>USA</th>
<th>Ecuador</th>
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<tbody>
<tr>
<td>BMI &gt;25Kg/m²</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>BMI &lt;20 Kg/m²</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>
Dietary Strategies to Improve Immune Response in Elderly

- Micronutrients Supplementation
- Modifying level and type of macronutrients
- Calorie restriction
- Modifying non-nutrient Component of the diet
  - Phenolic compounds
  - Prebiotics
  - Probiotics
Vitamin E and Immune Response in the Aged

- Vitamin E supplementation of healthy elderly significantly improves in vivo and in vitro indices of T cell-mediated function.

Meydani et al. AJCN 1990; 52:557-563
Meydani et al. JAMA 1997; 277:1380-1386.
Relationship Between Blood Vitamin E Levels and Change in DTH

# Experimental Design

<table>
<thead>
<tr>
<th>Design:</th>
<th>Double-Blind, Placebo-Controlled, Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration:</td>
<td>1 year</td>
</tr>
<tr>
<td>Treatment:</td>
<td>200 IU/Day Vitamin E or Placebo</td>
</tr>
<tr>
<td>Subject:</td>
<td>617 Male and Female, Nursing Home Residents ≥65 years old</td>
</tr>
<tr>
<td>Main Outcome:</td>
<td>Upper and Lower Respiratory Infections</td>
</tr>
</tbody>
</table>
Vitamin E reduces the risk of acquiring respiratory infections

<table>
<thead>
<tr>
<th></th>
<th>% risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All respiratory Infections</td>
<td>35%</td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>38%</td>
</tr>
<tr>
<td>Common cold</td>
<td>37%</td>
</tr>
</tbody>
</table>

Vitamin E significantly reduces upper respiratory infections, in general, and common cold, in particular, in elderly.
• In human studies, not all of the elderly who receive supplemental vitamin E experience an improvement in immune response.

“Responders” & “Non-responders”

• Variability in response can not be fully explained by vitamin E status.
• Vitamin E treatment did not have an overall effect on TNFα production
Genetics influence cytokine production

- There is a high degree of variability in cytokine production between healthy individuals
  - Genetic factors may explain variability in cytokine production

- SNPs may account for individual variability
  - Single nucleotide polymorphisms (SNPs) are single base pair changes in the DNA.
  - Identified at genes that encode cytokine proteins.

SNP → influence cytokine response → impact infection
The effect E on TNF-\(\alpha\) production depends on TNF-\(\alpha\) -308G>A

- Interaction: vitamin E and TNF-a -308G>A
  \[ p=0.039^* \]

*Adjusted for baseline TNF-\(\alpha\) production

Placebo n=56 (G/G =46; A/G and A/A =10); Vitamin E group n=39 (G/G=22; A/G and A/A =17)

Belisle et al. J. Nutr., 2009
Conclusions

• These observations suggest that individual immune responses to vitamin E supplementation are in part mediated by genetic factors.

• Because A allele at TNFα is associated with higher TNFα levels, our observation suggest that the antiinflammatory effect of vitamin E is specific to those genetically predispose to higher inflammation.
## Nutritional Status (% deficient)

<table>
<thead>
<tr>
<th>Measure of Deficiency</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin (ng/mL)</td>
<td>&lt;20</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Copper (mg/dL)</td>
<td>&lt;55</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Zinc (mg/dL)</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>

**Placebo**

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Measure of Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>0</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
</tr>
<tr>
<td>Zinc (mg/dL)</td>
<td>31</td>
</tr>
<tr>
<td>Copper (mg/dL)</td>
<td>6</td>
</tr>
</tbody>
</table>

Age and Zinc Deficiency Have Similar Impact on Immune System

Pro-inflammatory cytokines

- **IFNα**
- **IL-10**

**APC**

**Th1**

- **IL-2**
- **IFNγ**

**Th2**

**B cell**

**Lymphocyte**

**Proliferation**

**Thymic Involution**

Reduced help for Ig class switch

Unspecific B cell activation

**Decreases with age**

**Increases with age**

**Effect of Zinc**

Adapted from Haase et al. 2009, Immunity & Ageing
### Serum Zinc levels and Pneumonia in Elderly Nursing Home Residents

<table>
<thead>
<tr>
<th>Pneumonia</th>
<th>Final Serum Zinc Groups</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥70ug/dl (n=310)</td>
<td>&lt;70ug/dl (n=110)</td>
</tr>
<tr>
<td>Incidence (# per person-yr)</td>
<td>0.25</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration (Days per person-yr)</td>
<td>3.19</td>
<td>6.82</td>
</tr>
<tr>
<td>Antibiotic prescriptions (# per person-yr)</td>
<td>0.26</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of antibiotic use (Days per person-yr)</td>
<td>2.50</td>
<td>4.85</td>
</tr>
</tbody>
</table>

Meydani et al. AJCN, 2007
In summary

• Low serum zinc in nursing home elders is associated with increased severity, incidence and duration of pneumonia, suggesting they would benefit from zinc supplementation.

• The efficacy of zinc supplementation of zinc deficient nursing home elders to reduce prevalence of pneumonia needs to be assessed. But, before such a study is conducted....
Goal of Pilot Study

• **Primary:** To demonstrate that supplementing 30 mg/day of zinc gluconate plus 1/2 DRI of majority of the essential vitamins and minerals for 3 months will result in an increase in serum zinc levels, comparing to those in the placebo group, who will receive a similar capsule but with 5 mg/day of zinc.

• **Secondary:** To determine the impact of zinc supplementation on T cell-mediated immunity.
Study Design

Total Recruits (>65 years) (N=442)

- Excluded (N=389)
- Screen for Zinc < 73 μg/dl (N=53)
  - No (N=22)
  - Yes (N=31)
    - 6 withdrew from study
      - Placebo (5mg/d Zn) + 1/2 DRI (N = 13)
      - Supplement (30mg/d Zn) + 1/2 DRI (N = 12)

Baseline → Month 3

Blood draw for serum zinc and immune parameter measurement
Baseline values do not differ between zinc and placebo group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=13)</th>
<th>Zinc (N=12)</th>
<th>P &lt; 0.05</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>84.5 ± 9.4</td>
<td>87.4 ± 5.6</td>
<td>N</td>
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<tr>
<td>Women (N)</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Men (N)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6 ± 5.4</td>
<td>26.2 ± 7.7</td>
<td>N</td>
</tr>
<tr>
<td>Zinc (ug/dl)</td>
<td>67.3 ± 9.9</td>
<td>63.6 ± 10.4</td>
<td>N</td>
</tr>
<tr>
<td>Copper (ug/dl)</td>
<td>104.4 ± 19.9</td>
<td>111.3 ± 16.6</td>
<td>N</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7 ± 0.3</td>
<td>3.8 ± 0.6</td>
<td>N</td>
</tr>
<tr>
<td>Globulin (g/dl)</td>
<td>2.8 ± 0.5</td>
<td>2.7 ± 0.5</td>
<td>N</td>
</tr>
<tr>
<td>Total Protein (g/dl)</td>
<td>6.4 ± 0.5</td>
<td>6.5 ± 0.6</td>
<td>N</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>5.1 (1.8-34.6)</td>
<td>5.2 (0.2-40.8)</td>
<td>N</td>
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</table>
Serum zinc significantly increased in supplemental group

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>Month 3</th>
<th>Change</th>
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<tr>
<td>Placebo</td>
<td>67</td>
<td>65</td>
<td>↓ 2</td>
</tr>
<tr>
<td>Zinc</td>
<td>64</td>
<td>73</td>
<td>↑ 9</td>
</tr>
</tbody>
</table>

*P=0.006  (Baseline vs. Month 3)

**P=0.004  (Placebo vs. Supplemented)

Mean and SEM shown
Lymphocyte Proliferation Increased in Zinc Group

**Stimulation with anti-CD3/CD28**

- Placebo: BS, M3
- Zinc: BS, M3

**Stimulation with PHA**

- Placebo: BS, M3
- Zinc: BS, M3

p<.05
Zinc change is correlated with change in lymphocyte proliferation

Analysis: Pearson Correlation Coefficient

r = 0.52
p = 0.02
Zinc Supplementation Increased WBC and CD4/CD8 Ratio

(WBC) Placebo vs. Zinc (Mean ± SEM) p<0.05

(CD4 / CD8) Placebo vs. Zinc (Mean ± SEM) p<0.05
Conclusions

• Supplementation of zinc-deficient nursing home elderly with 30 mg/day Zn for 3 months significantly increases serum zinc levels and improves T cell function as measured by increased lymphocyte proliferation and enhanced CD4/CD8.

• Future studies are needed to determine whether these changes translate into reducing the incidence and duration of pneumonia in nursing home elderly.
Zinc Supplementation of Older Adults Might Reduce Infection

- A study conducted in a small number of elderly showed that those who were supplemented with zinc (45mg/d) for a year had 65% less infection compared to the placebo.

Nutrition and Immune Response in Elderly: Lipids

- Fish Oil
- Black Currant Seed Oil
- Trans Fatty Acids
- Caloric Intake
Modulatory Effect of EPA on Eicosanoid Synthesis

Diet → AA → membrane phospholipids

EPA

LOX → LTB₅
COX → PGE₃

LOX → LTB₄
COX → PGE₂

PLA₂

Less inflammatory
Inflammatory
Experimental Design

Ave. American

6

2

In vitro testing

DTH

NCEP-2 Low or High Fish

24 weeks

In vitro testing

DTH

6

2

weeks
Effect of Low-fat Diets High and Low in Fish on Ex-vivo Cytokine and PGE$_2$ Production

<table>
<thead>
<tr>
<th></th>
<th>Low fat, high fish</th>
<th>low fat, low fish</th>
<th>% change</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1$\beta$</td>
<td>-40*</td>
<td>62*</td>
<td></td>
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<tr>
<td>TNF</td>
<td>-35*</td>
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<td>IL-6</td>
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<td>-63*</td>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# Compared to their own baseline

Meydani et al., JCI; 92:105-1, 1993
Effect of Diets High and Low in Fish on DTH


* Significantly different from before
Groups

• All groups received 5 capsules/d of Omega-500TM (providing 1.5 g EPA, 1 g DHA, and 5 IU vitamin E/d)

• Each group received a capsule for 100, 200, or 400 IU/d dl-α-tocopherol, respectively, for 3 months.
**Vitamin E Supplementation Increases DTH in Subjects Supplemented with Fish Oil**

Vitamin E Supplementation

<table>
<thead>
<tr>
<th>Supplementation groups</th>
<th>48 h induration (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>3-mo</td>
<td>30 ± 3</td>
</tr>
<tr>
<td><strong>Vit E 100</strong></td>
<td>25 ± 3</td>
</tr>
<tr>
<td><strong>Vit E 200</strong></td>
<td>30 ± 3</td>
</tr>
<tr>
<td><strong>Vit E 400</strong></td>
<td>25 ± 3</td>
</tr>
</tbody>
</table>

Mean ± SE, n=8 to 10/group

*p<0.05 compared to the baseline

Wu et al. JACN, 25: 300, 2006
Vitamin E Decreases LPS-Stimulated IL1-β Production in Subjects Supplemented with Fish Oil

Wu et al. JACN, 25: 300, 2006
Nutrition and Immune Response: Caloric Intake
Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy

CALERIE

Jean Mayer USDA HNRCA at TUFTS UNIVERSITY
BOSTON, MA
Experimental Design

• **Design:** Randomized, controlled, single-blind

• **Subjects:** Men and women, 25-45 years old, with BMI of 25-29 Kg/m²

• **Intervention:** 10 or 30% calorie restriction.

• **DTH:** Baseline and after 6 mo.

• **In vitro immune measures:** Baseline and after 6 mo.
Effect of Calorie Restriction on Delayed Type Hypersensitivity Skin Response

Ahmed et al. J. Gerontology, 2009

* Significantly different from baseline
Effects of Calorie Restriction on Lymphocyte Proliferation

**Anti CD3**

![Chart showing proliferation under different conditions](chart1.png)

**ConA**

![Chart showing proliferation under different conditions](chart2.png)

**PHA**

![Chart showing proliferation under different conditions](chart3.png)

* Significantly different from baseline

Ahmed et al. J. Gerontology, 2009
Effect of Calorie Restriction on LPS-Stimulated PGE$_2$ Production

* Significantly different from baseline  

Ahmed et al. J. Gerontology, 2009
Nutrition and Immune Response in Elderly: Other Dietary Components

- Probiotics
- Prebiotics
- Wolfberry
Probiotic Studies

Daily Ingestion of Probiotics Improves Innate Defense Capacity in Healthy Middle Aged People

Increase in Elderly Immune Response with Specific Probiotic in 9-week Trial
Effect of Bifidobacterium lactis HN019 on Elderly Immune Response

Daily Ingestion of Probiotics Reduces Duration and Severity of Common Colds
What is Wolfberry?

- Wolfberry (Goji Berry) has long been used in China as a folklore medicine.
- A milk-based wolfberry preparation, called “Lacto-Wolfberry” (LWB) was recently reported to enhance the immune response in mice.
- However, it is not known whether the enhancement of immune response induced by LWB has a clinical relevance, e.g., increasing the host resistance to viral infection.
Influenza

- Influenza virus infection remains a significant public health problem.

- Immune function plays a key role in preventing and controlling microbial infection.

- However, there are limited strategies available to efficiently modulate host response to influenza.
Objective

To examine the effect of dietary supplementation with LWB on the host immune response and resistance to viral infection using a mouse influenza infection model.
Materials and methods

C57BL/6 male mice (4 mo)

5% LWB diet

Control diet

Infected with P/R 8/34 virus (H1N1)

4 wk

Killed mice at day 0, 2, 6, 9 postinfection and collected lung, spleen, liver and serum
Materials and Methods

• Lung and spleen cell isolation

• Lung viral titer by Madin-darby canine kidney (MDCK) assay

• NK cell cytotoxicity by $^{51}$Cr release

• T cell proliferation by 3H thymidine incorporation
Materials and Methods

• Cytokine production by ELISA

• FACS and immunophenotyping

• Statistical analysis by ANOVA followed by post hoc mean comparison
Summary

- LWB supplementation had a modest effect on reducing lung influenza viral titer. However, it was effective in attenuating the influenza symptom (weight loss) and lung pathology in mice.

- The mice fed with LWB had significantly higher Con A-stimulated T cell proliferation, IL-2, and INFγ production compared to the control mice on day 6 postinfection, and no difference in NK activity.

- LWB supplementation reduced TNF-α and IL-6 level in lung at day 6 postinfection.
Summary

- There was a significant correlation between weight loss, viral titer, pathology score, and T cell function.

- There was a significant correlation between weight loss and TNF alpha, and IL-6 production.

- LWB improved antibody response to influenza in old mice. Could LWB supplementation prior to vaccination increase resistance to influenza infection in elderly?
Conclusions

- Deficiency of nutrients as well as aging can impair host defense and increase virulence of pathogens – presenting a public health challenge world-wide.

- Nutritional strategies can be devised to optimize host resistance resulting in significant saving in health care cost.
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