Exercise, Immunity & Aging

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An Exercise Story

I started playing tennis and skiing in my forties. On a skiing trip, I broke a rib. The doctor said my spine was so bad he did not know how I did anything. I tried to stay active as long as possible. As the years passed, I developed bad back pain. The doctor said he could not help me, that I was too old. Also, I was diagnosed with emphysema. I could not breathe well and was wheezing. The doctor said I would never improve. I thought I would never climb stairs again. I tired easily. I tried an exercise program at a local medical center. For six weeks, I worked out three times a week, two to three hours a day. I did weight training, treadmill, bicycle and breathing exercises. Even when I felt bad, I kept at it. I never let anyone discourage me. Eventually, the wheezing stopped, my breathing improved and the back pain disappeared. I was able to walk with energy to spare! I exercise regularly. My doctor says he has never seen anyone "get better!" I attribute my improvement to exercise.

| Name:  | Grace |
| Age:   | 91    |
| Location: | California |
| Activity:    | Walking, Yoga, Tennis, Weight Lifting |
Exercise, aging and non-infectious disease

- Heart disease
- Hypertension
- Diabetes
- Obesity
- Osteoporosis
- Alzheimer’s
- Stroke
- Cancer
- Osteoarthritis
- COPD (emphysema)
- Frailty/disability
- Renal disease
- Depression
- Anxiety
- Falls/balance
- Cognition
Effect of exercise on infectious disease / immunity

- Clinical evidence for immunologic dysfunction in older populations

- **FIRST APPROACH:** Pilot study

- Goal: To develop preliminary data in support of hypothesis (mouse or human model?)
Influenza / Pneumonia

• 7th leading cause of death in U.S. (all ages)
• 5th leading cause of death (age 65+)
• 3rd leading cause of death (age 85+)
• ~ 40,000 deaths annually
• >90% of mortality in individuals > age 65
• Influenza vaccine efficacy rates 70-90% in young, and only 17-53% in old (Goodwin K. 2006)
Influenza Virus Types A, B, C

Virus Structure
8 segments of ss RNA inside
- HA = hemagglutinin
- NA = neuraminidase

3 Virus Strains in seasonal vaccine
A/New Caledonia/20/99 H1N1, (A/California/7/2009 H1N1)
A Pananama/2007/99 H3N2, (A/Perth/16/2009 H3N2)
B/Hong Kong/330/2001 (B/Brisbane/60/2008)
Antibody response to vaccination

Pilot study

- Survey physical activity, collect blood post-immunization to assess antibody level

  - Active: exercise ≥ 3 times/week, with increase in heart rate, breathing, sweat
  - Moderately active – some exercise, but at lower amount or intensity than active group
  - Sedentary – no physical activity
Intervention Study – Phase I randomized controlled trial

(Subjects all sedentary initially)

• Exercise treatment group (3x wk, ~1 year)
• Control sedentary group
• Young adults (age comparison)

– Vaccination pre/post intervention
*Exercise and the J curve theory*

- None
- Moderate
- Exhaustive

Risk of Infection
Exercise treatment 10 months

Control treatment 10 months

Pre-vaccine blood

4wk post blood

12wk post blood

Pre-vaccine blood

4wk post blood

12wk post blood

Influenza Vaccine #1

(Young subjects)

Influenza Vaccine #2
Exercise improves antibody response to vaccination in older adults

Change in Influenza A H1N1 Antibody titer from pre-immunization

Change in Influenza B Antibody titer from pre-immunization
This measure of the cytotoxic T cell’s ability to destroy influenza-virus infected cells was improved by moderate aerobic exercise in older adults.

Cytotoxic T cell function

Granzyme B (units/mg protein)

- H1N1
- H3N2
- B

CON-OLD
EX-OLD
YOUNG

* *
Summary Phase 1

- A long-term aerobic exercise intervention increased antibody response to influenza vaccine (Influenza A H1N1 & H3N2). Antibody levels remained lower than young adults.

- Cytotoxic T cell function against Influenza virus was improved by exercise, and reached levels similar to young adults. (Cytotoxic T cell important in viral clearance)

- Depression, stress did not mediate effects of exercise
Intervention Study – Phase 2 randomized controlled trial multi-site (DMU & ISU)

- Aerobic Exercise treatment group (n=50)
- Flexibility/strength treatment group (n=50)
  - Vaccination pre/post intervention
  - Inflammation assessment
  - Psychosocial factors
How might exercise alter immunity/inflammation?

Exercise

Psychosocial factors

Immune response

Neuroendocrine factors
Psychosocial factors generally improved with either type of exercise intervention

<table>
<thead>
<tr>
<th>Group</th>
<th>FLEX-Strength</th>
<th>CARDIO-Aerobic</th>
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<tbody>
<tr>
<td>Time</td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>Depression</td>
<td>3.2±0.4</td>
<td>2.8±0.4*</td>
</tr>
<tr>
<td>PSS (stress)</td>
<td>14.2±0.8</td>
<td>14.8±0.9</td>
</tr>
<tr>
<td>Sense coherence</td>
<td>75.1±0.9</td>
<td>77.5±1.0*</td>
</tr>
<tr>
<td>LOT optimism</td>
<td>61.7±0.8</td>
<td>62.8±1.2*</td>
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Obesity (BMI>30) was associated with decreased antibody response to influenza immunization (pre-intervention)
Antibody response to vaccine after the exercise intervention is dependent on improvement in fitness
T cell response to vaccine after the intervention is associated with change in fitness and obesity.
Summary of vaccine response

- Overall improvement in aerobic fitness rather than specific type of exercise is associated with increased antibody response to vaccine in both obese and non-obese subjects.

- T-cell response to vaccine was greater in subjects that improved aerobic fitness regardless of exercise treatment, and lower in obese subjects.
Impact of exercise intervention on serum inflammatory factors

- Type of exercise
- Role of psychosocial factors
- Role of neuroendocrine (catecholamines)
Serum “inflammatory” IL-6 reduced by cardio-aerobic exercise
Serum "inflammatory" IL-18 reduced by cardio-aerobic exercise.
Serum C-reactive protein reduced by cardio-aerobic exercise
Summary of exercise and inflammatory factors

• Cardio-aerobic exercise reduced serum inflammatory factors to greater extent than flex/strength exercise

• The effect of exercise on inflammatory factors was independent of changes in psychosocial factors, catecholamines, and body fat.
Influenza Infection

1) Does exercise protect against infection with live virus?

2) Mechanisms?
Influenza Infection i.n.

Chronic exercise training (45min/d, 5d/wk, 12wks)

24 hr rest

Acute exercise 45 minutes 1X

Rest 12 weeks

Control treatment (rest 12 weeks)

Euthanize
Body weight loss resulting from infection was reduced to greatest extent in chronic exercised mice.
The viral load in lungs was reduced by both acute and chronic exercise.
Multiple inflammatory factors in the lung were reduced by both acute and chronic exercise at in lung 2 days post infection.
By day 5 post-infection, only chronic exercise showed a benefit in terms of reduced inflammatory factors.
Aged mice – is benefit of exercise present?

• Aged BALB/c mice (16-17 months of age)
  – Exercise: 5 d/week, 45 min/day, moderate intensity for 8-12 weeks; infected 24 hours after last exercise session
  – Non-exercise: exposed to similar noise/handling stress; infected at the same time as exercised mice

• Young BALB/c mice (2 months of age)
  – Age control comparison group, infected at same time as aged mice
Lung viral load was reduced by exercise in aged mice

BAL viral titer Day 4 post-infection

- uninfected
- NON-EX
- EX
- Young

Log BAL viral titer vs. BAL titer

* indicates statistical significance.
Multiple inflammatory factors in the lung were reduced in the exercised mice.
Lung lesion scores (tissue damage) was reduced in exercised mice by day 10.
Exercise was associated with reduced serum anti-influenza antibody

Serum anti-influenza IgM and IgG - 7 days post-infection

Optical density at 405nm

uninfected
NON-EX
EX
Col 8

IgM-DAY 7
IgG-DAY7
IgG-DAY10
Summary of mouse studies

• Viral load in the lungs of exercised mice is reduced – (as early as 12 hours post-infection)

• Symptom severity is reduced in exercised mice

• Levels of lung inflammatory factors and immunopathology (tissue damage) are reduced by exercise treatment.

• Serum anti-influenza IgG antibody is reduced by exercise, and may reflect reduced viral load

• There is a short term benefit to one single session of exercise just preceding exposure to virus.
**Acute exercise benefit in humans?**

- Single session of exercise immediately following vaccination
- Young adults – 2009, pandemic H1N1 (A/California/7/2009) vaccine
Exercise-moderate 90min; 1x

No exercise; rest 90 min

2 wk

4 wk

Blood collection

Immunization
H1N1 monovalent vaccine
Serum IgG antibody response to influenza vaccine was increased by a single session of exercise post-immunization.
Clinical implications?

• Moderate aerobic exercise in older adults appears to be more effective at reducing serum inflammatory factors than strength/flexibility exercise. (Many chronic diseases have inflammatory component).

• An overall improvement in aerobic fitness in obese and non-obese individuals (rather than type of exercise) is associated with improved immunity to vaccine.

• Obesity impairs immune response to vaccination.
Clinical Implications?

• Regular moderate exercise, as well as a single session of exercise improve host resistance to respiratory infection with influenza virus.

• One mechanism of improved host resistance involves an early reduction in lung viral load.

• Exercise at the time of immunization may improve antibody response to vaccine
Thank you!!!