Exercise and immunity: How much is right?

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Outline

• Exercise and Immunity
• Immune effects of exercise
• Epidemiology of exercise and infection
• Exercise & nutrition
• Exercise and stress
• Recommendations

The “J” curve
Organization of the Immune System

Anatomical and Physiological Barriers
- Lysozyme in tears and saliva
- Ciliary clearance
- Intact skin
- Low stomach pH

Innate Immunity
- TLR’s
- NLR’s
- Complement
- Host defense peptides

Adaptive Immunity
- Dendritic cells
- T cells
- B cells

Timing:
- 0-4 hours
- 4-96 hours
- Late > 96 hours
Deep puncture wound

Infection

Recognition by specific nonspecific
infector

Removal of infectious agent

Infection

Recruitment of effector cells

Recognition, activation, and differentiation by effector cells

Renewal of infectious agent

Infection

Transport of antigen to lymphoid organs

Recognition by type B and T cells

Renewal of infectious agent

Recognition mechanisms of innate immunity

Rapid response (hours)

Fixed

Limited number of specificities

Constant during response

Recognition mechanisms of adaptive immunity

Slow response (days to weeks)

Variable

Numerous highly selective specificities

Improve during response

Common effector mechanisms for the destruction of pathogens
Acute Effects of Exercise on Immunity

• Acute prolonged strenuous exercise is associated with transient suppression on immune function*
• Similar to the effects of infection, trauma, sepsis
• Correlated with 2-6x increase in self reported URI after an endurance event vs. trained non-competing controls

International Society Exercise+ Immunology Pt 1+2 ; 2011

Acute Effects of Exercise on Immunity

• Innate enhance NK activity
  - NK activity higher during training season than off season
  - No increase in NK with moderate training
• Neutrophil function suppressed
  - Returns to normal in most but may stay suppressed

Nieman, D Immunol an Cell Biol 2000;78,498
Acute Effects of Exercise on Immunity

- Increase cytokine release TNF, IL1, IL6
- Increased buffers IL10, IL1ra
- Increased APR – CRP others
- Hormonal changes
  - Increased epinephrine, cortisol, GH
  - May be driven by muscle derived IL6

Acute Effects of Exercise on Immunity - ADAPTIVE

- Prolonged exercise depresses lymphocyte counts transiently
- Decreased CD4/CD8
- Decreased TH1 with preserved TH2
  - Decreased LPA to mitogens
- Mobilization of memory T cells
- Immunoglobulin production inhibited
Acute Effects of Exercise on Immunity

Limitations

• Difficult to extrapolate ex vivo systems (i.e. LTT etc.) with non specific stimuli to host defense
• PB is only 0.2% of all leukocytes
• No instruments that can clearly correlate small changes in ex vivo systems to integrated host defense

Chronic effects of Exercise training on Immunity

• Most ACUTE exercise studies show return to baseline in 24 hours thus it is more important to ask what may be the “training effects” of exercise on immunity
• Cross sectional studies using common immunologic assays generally show athletes and non athletes to be similar (with some showing increased NK activity)
• No effect of moderate exercise on vaccine response or DHT (Med Sci Sport Ex 29:1176,1997)
Chronic effects of Exercise training on Immunity

- The same “immunosuppression” seen with acute severe exercise in non-athletes is seen in highly trained athletes but these subjects are not immunodeficient.
- Acute exercise has little effects on mucosal immunity but prolonged exercise does and may correlate with increased infections.


Exercise effects on mucosal immunity
Maree Gleeson and David B Pyne
Immunology and Cell Biology (2000) 78, 536–544;

Pre-exercise salivary IgA concentrations for each training session over a 2 week period for an elite kayaker and the percentage change from the initial concentration.
Training volume and upper respiratory tract illness (URTI) episodes during a spring-summer training and competition season for elite swimmers (n = 22). Each shaded block indicates an episode of URTI in a swimmer.

EPIDEMIOLOGY OF INFECTIONS AND EXERCISE/TRAINING

- Studies in 80s and 90s (Peters + Bateman, Neiman others) demonstrated increased URI following marathons vs. matched controls (100-500%)
- Not confirmed by all
- Most not clinically confirmed
The “J” curve

EPIDEMIOLOGY OF INFECTIONS AND EXERCISE/TRAINING

• More recent studies (elite, competitive, untrained) using validated screening instruments and microbial isolation confirmed the “J” curve though pathogens found in only 30%
• Raises the issue of the nature of “URI’ in elite athletes i.e. allergic, vasomotor, other
Mechanisms of immune compromise with exercise

- Measuring immunity between athletes and non-athletes may not be as meaningful (clinically) as the magnitude of change that occurs with prolonged exercise creating an “open Window”
  - Decreased PMN function
  - Altered trafficking
  - Decreased mucosal immunity
  - Decreased NK function; LPA; DHT; APC

- 1002 adults were followed 12 weeks (winter fall) and monitored for URTI (Wisconsin URSS)
- Subjects reported frequency of aerobic activity and rated their fitness

RESULTS: Number of days with URTI symptoms was reduced 43% in subjects reporting 5 or more days of aerobic training; URTI severity was also reduced

CONCLUSION: Perceived physical fitness and frequency of aerobic training are important correlates of reduced days of URTI and severity in fall/winter

OTHER STUDIES 29% decrease with moderate to vigorous physical activity (Matthews MED SCI SP EX 2002)

Upper respiratory tract infection is reduced in physically fit and active adults.
Nieman DC, Henson DA, Austin MD, Sha W.

DESIGN:
A group of 1002 adults (ages 18-85 years, 60% female, 40% male) were followed for 12 weeks during the winter and fall seasons while monitoring URTI symptoms Subjects reported frequency of aerobic activity, and rated their physical fitness level.

RESULTS
The number of days with URTI during the 12-week period was significantly reduced, 43% in subjects reporting ≥ 5 days/week aerobic exercise

CONCLUSIONS: Perceived physical fitness and frequency of aerobic exercise are important correlates of reduced days and severity for URTI
Physical activity and immune function in elderly women


- Women 67-85 randomized to walking and calisthenics
- Immune function; Aerobic capacity and URTI were monitored

- RESULTS: Incidence of URTI was lowest in the highly conditioned group and highest in the calisthenic control group during the 12-wk study, with the walkers in an intermediate position (chi-square = 6.36, P = 0.042). In conclusion, the highly conditioned elderly women in this study had superior NK and T cell function when compared with their sedentary counterparts.

Anti-inflammatory effects of exercise

- Healthy diet and physical activity
- Positive energy balance and physical inactivity
- Pro-inflammatory cytokines (IL-6, IL-1)
- Free fatty acids
- TLK expression

- Chronic low-grade inflammation
- Increased risk for atherosclerosis, type 2 diabetes, neurodegeneration and cancer growth
- Reduced functional capacity
- Reduced longevity
Exercise and Nutrition

- Nutrition and exercise are intimately linked and raise the question of the impact of select macronutrients on IR
- CHO (30-60gr/hr.) attenuates IL6, catecholamines an cortisol and attenuates post exercise immunosuppression
- Vit C (500mg/day) and Vit E (400IU/day) (SBPC) attenuated IL6 release from muscle with acute exercise
- Most studies of other nutrients (AA, protein, PUFA, etc) are negative

Gunzer et al Nutrients 2012;4:1187

Exercise and Stress

- Fight or flight
  - Short term beneficial (minutes/hours)
  - Long term deleterious (weeks/months)
- Mediated by numerous integrated physiologic systems i.e. HPA, immune other
  - Schedlowski (J Clin Imm 1993) measured T cells in parachute jumpers pre, post, delayed
    - Increased T NK immediately after (epi); suppressed 2 hrs after (cortisol)
Chronic stress and immunity

- Dysregulatory
  - Altered cytokine balance
  - TH1/TH2 skewing
  - Accelerated immunosenescence
  - Decreased numbers, trafficking and function of adaptive immunity
- Exercise that is prolonged, extreme etc can be deleterious and mimic chronic stress
- Exercise that is ‘appropriate’ can be beneficial and serve to de-stress

Chronic stress and immunity

- Beneficial effects of exercise on stress are more likely to occur when:
  - Physical and psychosocial aspects of exercise are matched (fitness, capability, temperament, etc) of the individual
  - Highly individual!
Pathogenesis and Natural History and Latency of VZV

- Can not be cultured
- + S blot and PCR
- neuronal - epineuronal cells
- episomes
- select gene expression

Dermatomal VZV

- Re-activation of VZV, 1,000,000/yr
- Lifetime risk 10-20% and greater if > 85
- Risk increases with age - 10x > 60yoa
- Recurrence rate < 5%
- thorax > Cr n V, other areas and Cr n
- Post herpetic neuralgia in older patients, motor involvement, super infection, ocular spread, CNS
Viral Replication Results in Ganglionitis

Skin or mucous membrane

Pain perceived at skin or mucous membrane

Descending noradrenergic and serotoninergic inhibitory fibers

Ascending spinothalamic fibers

Pain perceived at skin or mucous membrane

Dorsal root ganglion

Immunosenescence

<table>
<thead>
<tr>
<th>Bone marrow</th>
<th>Thymus involution</th>
<th>Naive T cell</th>
<th>Memory T cell</th>
<th>Oligoclonal expansion</th>
<th>Clinical implications</th>
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<tbody>
<tr>
<td>Increased HSC number and self-renewal</td>
<td>Lower activity of HSC on a per cell basis</td>
<td>Low naive T cell output</td>
<td>Age impacts on thymocyte dynamics and turnover</td>
<td>Age impacts on lymphocyte dynamics and turnover</td>
<td>Detective response to infections and vaccines, pausible cancer</td>
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<tr>
<td>Attended by progressive immune activation</td>
<td>Oligoclonal expansion</td>
<td>Either antigen independent or antigen driven (CMV)</td>
<td>Dysfunctional cells fill the immunological space</td>
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Immunity to VZV age and depression

Immunity to VZV reactivation T cell - CMI
Tai Chi Chih

Tai Chi mind-body
Combines physical activity with modest aerobic component with “meditation through movement”
Associated with documented health benefits in multiple domains and the treatment of illnesses such as fibromyalgia
NEJM 2011

Tai Chi Chih
Westernized version

Shingles immunity and health functioning in the elderly: Tai Chi Chih as a behavioral treatment

15 weeks
Randomized
20 movements
45 minutes – 3 times /week
Health education control

After 16 weeks both immunized with VARIVAX
Quantitative measurements of VZV CMI and QOL (SF36)
RESULTS

- Tai Chi group showed higher levels of VZV-CMI than HE controls (2 x)
- Tai Chi alone increased VZV CMI that was comparable to varicella vaccine
- Tai Chi group improved in QOL physical function, pain, vitality, mental

- CONCLUSION Tai Chi Chih improves VZVZ CMI and augments VZV induced CMI from varicella vaccine
Exercise and Immunity
How much is right?

• J curve seems right
• Mind body exercise appears to have positive biologic effect
• Numerous unanswered questions
  - MOA
  - Dose
  - Timing