Exercise and Bone Mass
What’s the Evidence?
Is there a mechanism?

Clifford J Rosen MD
Maine Medical Center

Pyramid of Evidence

Systematic Reviews of RCTs & Meta-Analysis
Randomized Controlled Clinical Trials (RCT)
Cohort Studies
Case-Controlled Studies
Single Subject Design
Case Studies
Expert Opinion
Clinical Experience
Bench or Animal Research

Why Exercise! Is there Evidence?

- Increase bone mass pharmacologically
- Exercise provides two benefits

- Increase bone mass
- Decreased risk of falls

Strategy to Increase Bone Mass

- Maximize peak bone mass in the first three decades
- Minimize BMD decline after age 40 secondary to inactivity, endocrine changes, nutrition or other factors
- Exercise is one of the “other factors”
Bone Health and Exercise: Too Little and Too Much- Are They Related?

Too Little – osteomalacia & osteopenia
Zero gravity

Too Much – Stress fractures or amenorrhea

Exercise and Bone Mass Controversy

Controversy

Bone mass development and maintenance is multifactorial with nutrition and hormonal influences that can have a greater impact
Exercise prescription is unclear
No dose-response relationship has been confirmed in the developing skeleton nor for either the middle aged nor elderly

Pros

Absence of mechanical loading, gravity has been shown to cause a decrease
Active individuals have greater bone mass than sedentary individuals as shown in cross-sectional studies
Bone mass increases with activity in sedentary individuals in longitudinal studies
NASA is currently working on an Exercise Countermeasures Project to help promote the health and safety of astronauts and reduce the effects of zero gravity. They are studying and developing exercises that astronauts can do while in space. They are working to come up with equipment and workouts that are both time and space efficient. Some of the products of this program are depicted in the next few slides.

The astronauts do treadmill exercises that include walking, running, deep knee bends, and resistive exercises. These exercises are designed to stimulate bone mass, cardiovascular fitness, muscle endurance, and the neurophysiologic pathways and reflexes required for walking on Earth or other planetary surfaces.

The astronaut depicted to the right is doing “resistive training.” He is strapped into the device and weight is imparted on his body to help simulate the weight he would normally experience while on earth. This particular machine can impart up to 300 lbs of pressure.

What is he doing?

Image from NASA webpage
Developing Optimal Bone Mass

If exercise is beneficial then a number of questions arise:

- When and how do I begin developing optimal bone mass?
- Is exercise in infancy or prepuberty advised?
- Is exercise needed to be continued as part of a person’s lifestyle into adulthood?
- How much is enough?

Does Exercise Affect Bone Mass in Infants?

Yes, 5 randomized clinical trials provide evidence to support enhanced bone development in children using exercise as an intervention:

- Moyer-Mileur et al, 1995
- Moyer-Mileur et al, 2000
- Nemet et al, 2001
- Litmanovitz et al, 2003
- Aly et al, 2004

Positive effects of brown adipose tissue on femoral bone structure

Miriam A. Reddell, Cody M. Gill, Clifford J. Rosen, Anne Kilbanski, Martin Torriani

Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA
Korakakorn PhD, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA

Maine Medical Center Research Institute, Scarborough, ME 04074, USA

BAT is Related to Muscle Mass in Infants

Results of MRI comparison of BAT in the suprascapular area and paraspinous musculature in 12 infants. High fat proportion (FF) is due to in-growth of BAT into subcutaneous fat (data is based on an example of an MRI of a subcutaneous FF image of a supraspinatus in a 6 Day and 6 Month Infant). Age variability is notable throughout all age groups.
**Exercise & Bone Mass in Prematurity**

- Random assignment of 32 preterm infants
  - Birth weight of 800-1600 g & 26-32 wks gestation
  - Stratified assignment using birth weight & gestational age then randomly assigned to exercise or control
- 4 week exercise program
  - 5 repetitions of passive range of motion (ROM) with mild manual compressions to the wrist, elbow, shoulder, ankle, knee & hip
  - 5-10 minutes in duration, 5 days per week
- Control program with holding & stroking

Moyer-Mileur et al, 2000

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**Exercise & Bone Mass in Prematurity**

- Random assignment of 24 preterm infants
  - ≈1000 gr, 28 wks gestation, corrected age of 33 weeks at enrollment
- 4 week exercise program
  - 5 repetitions of passive ROM with mild manual compressions to the wrist, elbow, shoulder, ankle, knee & hip
  - 5-10 minutes in duration, 5 days per week
- Control program with holding & stroking

Nemet, et al, 2001

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**Exercise & Bone Mass in Prematurity**

- Significant difference between groups for serum type I collagen C-terminal propeptide (correlates with collagen turnover and bone formation in premature infants)
- Significant difference between groups for urine pyridinoline (marker for bone resorption)
- Significant increase in DEXA measures of:
  - forearm length & bone area,
  - BMC & BMD
Exercise & Bone Mass in Prematurity

- Significant increase in bone-specific alkaline phosphatase (BSAP), increase in C-terminal pro-collagen type I peptide & significant decrease in C-terminal type-I collagen telopeptide (ICTP)

Exercise & Bone Mass in Children and Adolescents

- Research evidence supports higher bone mass in children who participate in activities with high impact forces than sedentary controls:
  - Tennis (Haapasalo et al, 1996, Bass et al, 2002)
  - Gymnastics (Zanker et al, 2003)
  - Weight Lifting (Nichols et al, 2001)

Jumping & Bone Mass

- School-based Jumping in Girls (Petit et al, 2002)
- 14 schools in Canada with 383 girls
- Grades 4-6 (ages 9-12 years)
- 7 month program of jumping, 10 min/day, 3 times per week vs. regular activities
- Rated maturity with Tanner Scale
- Measured calcium intake & general physical activities
- DEXA scans of femoral neck, trochanteric & proximal shaft with calculation of:
  - Bone cross-sectional area
  - Cross sectional moment of inertia
  - Section modulus (indicator of bone strength)

Jumping & Bone Mass

- Results
  - No significant bone structure change in prepubertal girls (Tanner stage 1)
  - Significant bone structure change in early pre-pubertal (Tanner stage 2-3)
    - Increase bone cross-sectional area & section modulus due to less endosteal resorption & increased cortical thickness
    - No significant difference in periosteal width
Jumping & Bone Mass

- **Discussion**
  - Technology used allows for analysis of both structure (geometry) in addition to density
  - Jumping causes a primary compressive load
    - bone responds by increasing surface area & section modulus (bone deposition on the endosteal surface rather than increasing the diameter, i.e., greater cortical width)
  - Racket sports cause torsional and bending loads
    - bone responds by increasing overall width (cross-sectional area)

Tennis & Bone Mass

- **Discussion**
  - Study of pre-, peri- & postpubertal girls and effect of tennis (Bass et al, 2002)
  - 47 competitive tennis players, age 8-17 years, playing 3 hr/wk for at least 2 years
  - Cross-sectional design examining 3 age groups
  - T1 weighted MRI of mid & distal humerus & DEXA (BMC)

- **Results**
  - Tennis arm bone growth was found to be 14-20% greater than opposite arm
  - Tennis arm BMC and calculated resistance to torsion was 11-14% greater than opposite arm
  - Differences noted at mid vs. distal humerus
General Exercise & Calcium Effect

- 178 children age 3-5 years randomized to gross motor vs. fine motor with calcium vs. placebo groups
- 1 year intervention with exercise at day care, 5 day per week jumping or other high impact activities for 20 minutes
- Most significant increase in tibial bone density (pQCT) in exercise group with calcium supplementation

Specker & Brinkley, 2003

Exercise & Bone Mass in Twins

- Weight-bearing exercise in monozygotic twins (Langedonck et al, 2003)
- 21 prepubertal twins, mean age of 8.7 years
- Random assignment to exercise & control groups
  - Exercise with high-impact activities (rope skipping, hopping, jumping off raised surface) and general activities, 10 min, 3 times/week for 9 months
  - DEXA scans for aBMD & bone area (proximal femur, femoral neck and lumbar spine)

Exercise & Bone Mass in Twins

- Results
  - Similar growth (height & wt) between groups
  - Significant greater aBMD & BMC change of proximal femur in exercise vs. control group when control group twin was sedentary
  - Active control group twin vs. exercise twin did not show any significant differences for any bone indices
- Conclusion
  - Questionably adequate dosage of exercise

Specker & Brinkley, 2003
Am. College of Sports Med. Recommendations

- **Children & Adolescents**
  - **Mode** – impact activities (gymnastics, plyometrics and jumping and moderated resistance training), sports that involve running and jumping (soccer & basketball)
  - **Intensity** – high bone-loading forces & resistance training <60% of 1-rep. maximum
  - **Frequency** – 3 days per week
  - **Duration** – 10-20 minutes

  Kohrt et al, 2004

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Physical Activity and Adults

- **Meta-analyses are Available:**
  - Exercise & postmenopausal women (Bonaiuti et al, 2002) – Cochrane Library
  - Exercise in pre- and postmenopausal women (Wolff, 1999)
  - Resistance training in women (Kelly et al, 2001)

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Resistance Training & Adults

- **Meta-analysis of 29 RCT or CT (325 pre & postmenopausal female subjects)**
- **Synopsis of each article including training intervention used**
- **Overall results:**
  - Resistance training helped to preserve lumbar spine BMD
  - Training increased and preserved BMD at the femur and radius
  - The training effects were not large with generally small effect sizes across articles

  Kelley et al, 2001

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Physical Activity and Adults

- **Exercise & postmenopausal women** (Bonaiuti et al, 2002) – Cochrane Library
- **Reviewed of 18 RCT**
- **Synopsis:**
  - Aerobics, weight-bearing and resistance exercise are effective on BMD of spine. Walking is effective for the hip.
  - Quality of trials was low resulting in recommendation for additional studies.
  - Role of exercise in preventing bone loss in postmenopausal women remains unclear.
Physical Activity and Adults

- Exercise & postmenopausal women (Kelley 1998)
  - Reviewed of 11 RCT
  - Synopsis:
    - Exercise may slow bone loss in postmenopausal women.
    - Effect sizes ranged from 0.02 for aerobic exercise to 0.73 for strength training.
    - Quality of trials was low resulting in recommendation for additional studies.

Am. College of Sports Med. Recommendations

- Adults
  - Mode – weight-bearing activities (tennis, stair-climbing & walking), jumping activities (volleyball & basketball) & resistance activities (weight-lifting)
  - Intensity – moderate to high bone-loading forces
  - Frequency – weight-bearing endurance: 3-5 times per week; resistance exercise 2-3 times per week
  - Duration – 30-60 minutes per day of combined endurance and resistance activities

Kohrt et al, 2004

The New York Times
REPORTER'S FILE-2008
Does Exercise Really Keep Us Healthy?

Exercise Is Not the Path to Strong Bones
By GINA KOLATAAPRIL 1, 2016

Does Obesity Have an Impact on Bone Mass and if so How?
Converting White to Brown Fat: The New Pharmacology

Current Agents: Thiazolidinediones

Future Agents: FGF-21
Beta agonists
Irisin
Enriched Environment
Cold Temperature

IRISIN IS DERIVED FROM FNDC5 WHICH IS INDUCED BY Pgc1a

Irisin Increases Cortical Bone Mass- PNAS 2015

B6 Male In Vitro BMSC with Irisin Treatment

Experiment 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ALP</th>
<th>VK</th>
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<tbody>
<tr>
<td>Control</td>
<td>0.15</td>
<td>0.10</td>
</tr>
<tr>
<td>100 ng/mL</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>500 ng/mL</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>1000 ng/mL</td>
<td>0.30</td>
<td>0.25</td>
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</table>
Summary

- Exercise is great
- Exercise causes fat loss
- Exercise may alter brown fat
- Exercise reduces falls
- Exercise probably does not increase bone mass!!! But….
- In children yes
**Exercise Interventions in Pre-pubertal Children**

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<tr>
<th></th>
<th>Control</th>
<th>Exercise</th>
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<tr>
<td>TB</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>PF</td>
<td>3.2</td>
<td>4.2</td>
</tr>
<tr>
<td>L2</td>
<td>2.2</td>
<td>3.2</td>
</tr>
<tr>
<td>L4</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
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- Ca²⁺ supplemented at 1500 mg/d
- 3 d/wk; 45 min sessions for 11 mo
- jogging / stair climbing vs. weight training

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**Benefits of Exercise**

- Improve life expectancy
- Reduce the effect of chronic diseases
- Restore function to inactive adults
- Improve quality of older life

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**Comparison of Impact Exercise vs. Weight Training on Changes in BMD of Postmenopausal Women**

- Kohrt et al., J Bone Miner Res 12:1253, 1997
Terminology

- Aerobic exercise training (AET): large muscles move in a rhythmic manner for sustained periods
- Resistance exercise training (RET): muscles work or hold against an applied force or weight
- Moderate intensity: ↑ heart rate and breathing but still able to hold a conversation.

Aerobic Exercise Capacity

- Can improve functional capacity in older adults (3 times per week)
- Larger improvements typically observed with longer training periods (20-30wks) but not necessarily higher training intensities.

Cardiovascular Effects

- 3 or more months result in:
  - Lower heart rate @ rest and moderate exercise
  - Smaller rises in mean BP
  - Improvements in Oxygen uptake capacities of muscles
  - BP Receptors become more efficient

Body Fat

- Moderate intensity Aerobic exercise has been shown to be effective in reducing total body fat.
- However Aerobic exercise does not improve skeletal muscle growth or strength
Body Fat
- **BUT** Strengthening exercises ↑ muscle & ↓ Fat
- Systematic Review: older adults demonstrate ↑ muscle tissue of 10-62%

Bone Health
- Aerobic exercise does not increase bone density
- But may be effective in counteracting age-related losses in Bone Density in postmenopausal women

Muscle Mass & Strength
- Older adults can significantly ↑ strength

Muscle Power
- Power capabilities: Substantial ↑ in muscular power have been demonstrated after RET (e.g. stair climbing) in older adults
**Muscle Endurance**
- May determine an older adult’s functional independence
- Moderate-intensity improves endurance
- Moderate intensity: Patients with respiratory conditions & muscle weakness → Improved endurance

**Ageing and Exercise**
- Typical “ageing effects” are greatly influenced by regular exercise
- The precise extent is unknown
- Sedentary living: losses in functional capacity that are at least as great as the effects of aging itself

**Epidemiological Evidence**
- Strong association between regular physical activity / physical fitness and all causes of death

**Nursing Home Study**
- Strengthening exercises vs multinutrient supplementation: 100 frail nursing home residents over 10wks
- Mean Age 87.1 yrs; 83% cane or walker; 66% falls
- High-intensity Strengthening of hip & knee extensors 45 mins 3 days/wk
- Nutritional supplementation: 1/day → augment caloric intake by 20% & provide 1/3 of the RDA of vitamins and minerals.
Results

<table>
<thead>
<tr>
<th></th>
<th>Exercising Group</th>
<th>Non-Exercising Group</th>
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<tbody>
<tr>
<td>Muscle Strength</td>
<td>↑ 113±8%</td>
<td>↑ 3±9%</td>
</tr>
<tr>
<td>Walking Speed</td>
<td>↑ 11.8±3.8%</td>
<td>↓ 1.0±3.8%</td>
</tr>
<tr>
<td>Stair climbing power</td>
<td>↑ 28.4%</td>
<td>↑ 3.6%</td>
</tr>
<tr>
<td>Cross sectional thigh muscle area</td>
<td>↑ 2.7%</td>
<td>↓ 1.8%</td>
</tr>
</tbody>
</table>

Other Nursing Home Studies

- Large gain in strength (174%) & walking speed after 8 weeks
- Combination of isometric and low intensity weight lifting for 6 weeks→ gain in strength (15%)

Strengthening Exercises

- Can improve muscle size & strength in frail elderly people
- Improvement in mobility and an increased level of spontaneous physical activity can also be seen
- Subjects initially the weakest had the largest benefit

How much exercise is needed?

- Physical activity guidelines for older adults (65+) published 2011
- Older actives
- Older transitionals
- Older frail
How much is enough?
- 150 minutes per week
  or
  30 minutes x 5 days

  or for the frail...build up from 10 minutes per day.

  However.............

Physical Activity Guidelines
- Muscle Strengthening activities
  IN ADDITION TO
  the recommended 150 minutes per week

  But not every day! Twice per week.

Physical Activity Guidelines
- Balance and Co-ordination activities
  IN ADDITION TO
  the recommended 150 minutes per week

  AT LEAST TWICE PER WEEK!

Conclusion
- AHPs and Carers have the opportunity and responsibility to promote regular exercise.

- Regular exercise can minimise the damaging effects of sedentary living

- Combination of Resistive and Aerobic exercise

- SOME EXERCISE IS BETTER THAN NONE!
Does Obesity in Children Result in Fractures?

Obesity is a Risk Factor for Childhood Fractures

- Cross-sectional study of children age 3-19 years with no history of fracture
- 200 girls, 136 boys in New Zealand, all Caucasian
- Total body bone mineral content (BMC) and bone area (BA), as well as body composition measured by DEXA
- Results suggest a mismatch between rate of gain in adiposity and rate of gain in bone mass
- May accentuate the known mismatch between linear growth and bone mineral accrual in adolescents, further increasing the risk for fracture
- Not known whether this relative deficit persists into adulthood


SC Fat is directly related to CBA and PMI

Visceral Fat is negatively associated with trabecular BMD by QCT and positively with Muscle CSA

Gilsanz, 2009
Obesity: Increases in both trabecular and cortical bone

Obese Premenopausal Women have low BV/TV and decreased BFR by bone bx

Bariatric surgery

Weight loss after gastric bypass

Yu et al, JCEM in press

Wayne Stuberg, PT, PhD, PCS
Post-Congress Workshop, WCPT

http://www.asmbs.org/Newsite07/patients/benefits.htm

Cohen, et al JCEM 2014

Obese Premenopausal Women have low BV/TV and decreased BFR by bone bx

Eastell, JBMR, November 2014
Bone loss after gastric bypass: spine

Volume of pre-formed BAT directly related to BMD of spine, hip, total body r = 0.50-0.70; p ≤ 0.01, but also related to CSA of muscle

The New York Times
REPORTER’S FILE-2008
Does Exercise Really Keep Us Healthy?
Exercise Is Not the Path to Strong Bones
By GINA KOLATA
APRIL 1, 2016
Irisin Increases Cortical Bone Mass - PNAS 2015

Common Origins: Bone and Fat Arise from the Same Progenitor

- Myf5
- Pax7
- BMP7
- Beige cells
- Preformed BAT
- Pre-adipocytes
- adipocyte
- mesenchymal stem cell (mMSC)

Tibia and radius bone geometry and volumetric density in obese compared to non-obese adolescents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Difference (M1-M2)</th>
<th>p-value</th>
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<tr>
<td>Obese vs. non-obese</td>
<td>0.32 (-0.95 to 1.60)</td>
<td>0.60</td>
</tr>
<tr>
<td>Cell mass bone 2-score</td>
<td>0.05 (-0.89 to 0.99)</td>
<td>0.90</td>
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<tr>
<td>Abdominal visceral fat, per year</td>
<td>0.06 (-0.85 to 1.17)</td>
<td>0.93</td>
</tr>
<tr>
<td>Muscle strength 2-score</td>
<td>0.21 (-0.35 to 0.77)</td>
<td>0.93</td>
</tr>
<tr>
<td>Moderate to vigorous physical activity, per year</td>
<td>0.23 (-0.13 to 0.59)</td>
<td>0.26</td>
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