Bone Health in FSHD
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Baltimore
FSH Society

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FSHD
Facioscapulohumeral Muscular Dystrophy

• Inherited condition

• Weakness in FSH distribution

• Loss of strength and decreased muscle mass
FSHD is a muscle disease—Why do we care about bone?

- As muscle mass decreases, bone density decreases.
- With increasing muscle weakness, the chance of falling increases.

→ Increased Risk of Fracture
- Pain
- Loss of mobility
- Declining quality of life
Bone health is relevant to FSHD

- Bone physiology
- Bone health in the general population
  - Risk factors
  - Measure
  - Prevention
  - Treatment
- Bone health in Neuromuscular Disease
- Current Bone Health Study in FSHD
What is the Function of Bone?

Structural
• Protects our organs from injury
• Attach to our ligaments and muscles and allows us to move

Metabolic
• Reservoir for calcium and other minerals
Components of living Bone

- Composed of collagen and minerals
  - **Collagen** is a protein that provides a flexible framework
    - Layers of twisted fibrils
  - Calcium and phosphate are minerals that harden bone to withstand stress
Types of Bone in the Human Skeleton

• **Outer Cortical:**
  • dense and compact
  • resistant to bending

• **Inner Trabecular:**
  • less dense (honeycomb)
  • more elastic
  • increases in density during puberty.
  • decreases in density with age
Bone Growth is Dynamic Remodeling

• Bone is constantly being renewed as bone is removed and replaced

• The process of formation and resorption is called bone remodeling
Bone Remodeling Cells

• **Osteoblasts:** Formation
  cells that lay down new bone

• **Osteoclasts:**
  - large cells that *resorb* old or damaged bone
  - **Resorption** breaks down and removes bone.
Bone remodeling

**Formation**
- Osteoblast

**Resorption**
- Osteoclast
- Lining cells
Bone Remodeling varies with age

- **Childhood**: bone formation outpaces resorption
- **Young adult**: formation couples resorption
- **With aging**: resorption exceeds formation ➔ loss of bone mass
Determinants of Bone Mass

• Genetic predisposition

• Endocrine
  – Hormones

• Lifestyle
  – Diet
  – Exercise
Hormones

• Estrogen
  ▪ Protective effect on bone
  ▪ Prevents osteoclast formation ➔ less resorption
  ▪ With menopause, there is a decline in estrogen
    leads to accelerated bone loss in post-menopausal women

• Testosterone
  ▪ Inhibits bone resorption and maintains bone mass
  ▪ Low levels are associated with accelerated bone turnover and increased fracture risk
Hormones regulate bone remodeling

- **Parathyroid hormone** (PTH)
  - released when the [calcium] is low
  - stimulates bone formation.

- **Calcitonin**
  - produced by the thyroid gland.
  - stimulates bone formation
  - released when calcium is high
  - reduces osteoclast activity

FDA approved for the treatment of osteoporosis.
- PTH
- Calcitonin nasal spray
Diet - Nutrition
Calcium and Vitamin D

Vitamin D

• Needed for calcium absorption
• Calcium cannot be absorbed from the small intestine without vitamin D

• Rickets: Deficiency of vitamin D
  softening of the bones (osteomalacia)

• Levels can be measured by checking 25-hydroxyvitamin D₃

• Sources?
Vitamin D

Are you getting enough?
Sources of Vitamin D

**Sun** Exposure & Food

- Skin exposure to ultraviolet B radiation from the sun provides vitamin D.

- Requires direct exposure to sun without use of sunblock

“An individual in a bathing suit generates 10,000 to 25,000 IU of vitamin D2 after a minimal erythemal dose, which is the safest amount of radiation sufficient to produce redness in the skin…”

Holick et al J Bone Miner Res. 2007 Dec;22 Suppl 2:V28-33
Sources of Vitamin D

**Food sources**
- Fatty fish (salmon, tuna, herring)
- Eggs
- Fortified products
  - soy milk, almond milk, rice milk, orange juice, cereal
- Dietary supplements
Calcium

• Required for the maintenance of bone
• Needs change through the life cycle
• Peak nutritional needs
  – Adolescence and
  – During periods of rapid growth
Sources of Calcium

• Dairy
  Milk products, cheese, yogurt

• Non-dairy sources
  Fortified products
  • Soy milk, almond milk, rice milk, orange juice, cereal

• Tums
Sources of Calcium

- Broccoli
- Bok Choy
- Almonds
- Pumpkin Seeds
- Okra
- Collards
- Turnip Greens
- Prickly Pear
- Kohlrabi
- Leeks
- Brazil Nuts
- Artichokes
- Avocado
- Celery
- Green Beans
- Coconut Meat
- Onions
- Gooseberry
- Fennel
- Dandelion Greens
- Swiss Chard
- Spinach
- Kale
- Butternut Squash
## OPTIMAL DAILY CALCIUM INTAKE

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Recommended Dietary Allowance (mg/day)</th>
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<tbody>
<tr>
<td>1 – 3</td>
<td>700</td>
</tr>
<tr>
<td>4 – 8</td>
<td>1,000</td>
</tr>
<tr>
<td>9 – 18</td>
<td>1,300</td>
</tr>
<tr>
<td>19 – 50</td>
<td>1,000</td>
</tr>
<tr>
<td>51 – 70 males</td>
<td>1,000</td>
</tr>
<tr>
<td>51 – 70 females</td>
<td>1,200</td>
</tr>
<tr>
<td>71+</td>
<td>1,200</td>
</tr>
<tr>
<td>14 - 18 years old</td>
<td>1,300</td>
</tr>
</tbody>
</table>

Determinants of Bone Mass

- Genetic predisposition
- Endocrine
  - Hormones
- Lifestyle
  - Diet
  - Exercise
Lifestyle
Physical activity “Use it or lose it”

• **Exercise** promotes bone formation

• **Weight-bearing activities and mechanical stress** – promote ↑ bone mineral density

• Athletes in **high-impact** sports have greater bone density than those in **low-impact** sports
Lifestyle
Effect of Inactivity

- Prolonged bed rest and immobilization
  - inhibits osteoblast bone formation
  - accelerates osteoclast resorption
  - Resulting in bone loss
Mobility and Gravity are important for preserving bone mass!

• Mechanical stress and lack of gravity affect muscle and bone.

• Astronauts lose muscle and bone mass.
  Study: 13 astronauts on the ISS for 4.3 to 6.5 months
  • Reductions in proximal femoral bone strength comparable to a lifetime loss in Caucasian females*

Who is likely to have a fracture?

Risk factors

• Age > 65 both men and women
• Postmenopausal women: sharp decline in estrogen
• Ethnicity: Caucasian and Asian
• Family history of fracture
• Previous history of fracture
• Low body weight <127 pounds
• Smoking
• Alcohol >3 /day
• Certain drugs (steroids)
Figure 1. Incidence of osteoporotic fractures in women.

Incidence of osteoporotic fractures in men

Wasnich RD, Osteoporos Int 1997;7 Suppl 3:68-72
Can we measure bone health?

• Imaging

• Bone biomarkers
What is the utility of bone turnover biomarkers?

- Role in clinical management
  - Look at the turnover of bone indicating formation and resorption

- Role in research
  - Used to monitor outcomes in research studies
Best predictor for fracture

**Bone Mineral Density (BMD)**

BMD test: determines whether you have osteoporosis

* DEXA scan = *Dual-energy x-ray absorptiometry*

- Imaging technique of choice for measuring BMD
- Easy
- Minimal radiation

Two X-ray beams are aimed at the bones
Soft tissue is subtracted out
⇒ BMD is determined
Lean Body Mass (LBM)

- Can be estimated by DEXA

- With age, there is a decline in LBM and an increase in fat

- Suggestive evidence that lean body mass is positively correlated to bone mass*
  - Higher lean body mass (LBM) = more bone mass
  - Reduced fracture risk

*Kaji, H. J Bone Metab. 2014 Feb;21(1):29-40. Interaction between Muscle and Bone.*
Results of the DEXA scan

- Normal
- Osteopenia
- Osteoporosis

Values of Bone Mineral Density are in the form of T and Z scores.

“The Z-score at the left hip -3.8 ...”

- The T-score compares the patients’ BMD to the average for young adults at the time of peak bone mass
- The Z-score compares the BMD to persons of the same age.
Osteoporosis and Osteopenia

- “Osteo” is the Greek word for bone
- “- penia” is the Greek word for deficiency
- “- porosis” a porous condition (filled with holes)
Osteoporosis

• What is it?
  Loss of mineral and structural integrity of the bone

• Why do we care?
  Higher risk of fractures
Osteoporosis

Bone is fragile and prone to fracture
Osteoporosis and Osteopenia
Criteria set by the WHO
(World Health Organization)

• **Osteopenia** is defined as BMD between -1.0 and $-2.5$ SD in Z scores

• **Osteoporosis** BMD of $\leq -2.5$ SD

• Any fragility fracture = **Osteoporosis** regardless of the Z score
How can we reduce the risk of fractures?

- Lifestyle
- Nutrition
  - Calcium: If deficient, higher risk for osteoporosis
  - Vitamin D
    - Required for intestinal absorption of calcium
    - Blood Level varies by season and latitude
    - Sunblock decreases absorption of Vitamin D
- Pharmacology
Treatment for low BMD: Bisphosphonates

- alendronate (Fosamax) oral weekly
- risedronate (Actonel) oral daily, weekly or monthly
- ibandronate (Boniva) oral
- zolendronic acid (Reclast) IV once per year
- pamidronate (Aredia) every 3 months

- Oral agents are easier to take
  - Must be upright for at least 30 minutes with to reduce the risk of esophagitis
Bisphosphonates
Effective Rx for restoring BMD

• Reduce **bone resorption** by ↓ the activity of osteoclasts

• Side effects: flu-like symptoms especially with the first infusion, hypocalcaemia and osteonecrosis of the jaw

• Duration? After 5 years benefit of bisphosphonates not clear
Treatment of osteoporosis: Unresponsive or intolerant to bisphosphonates

• Anti-resorptive agents
  – Denosumab (Prolia)
    Antibody binds to a regulator of osteoclasts (RANKL) to inhibit bone resorption (SubQ every 6 months)

• Stimulate bone formation
  • Teriparatide hrPTH: Parathyroid hormone (Forteo)
    – Daily injection
      » can be used for up to 24 months
Bone Health in Neuromuscular Disorders

- Published data is limited
- Much of what we know comes from the \textit{Pediatric} neuromuscular literature

- Children with Spinal Muscular Atrophy (SMA) Duchenne Muscular Dystrophy (DMD)
  - Low bone density
  - Increased fractures
Bone health in boys with Duchenne (DMD)

- Fracture risk factors
  - Progressive muscle weakness
  - Limited weight bearing
  - Vitamin D deficiency
  - Use of corticosteroids

- Corticosteroids are associated with
  - Reduced osteoblast activity (↓ bone formation)
  - Increased osteoclast activity (↑ bone resorption)
Study: Use of Vitamin D in boys with Duchenne (DMD)

*Study over 3 years: 33 boys with DMD

➢ At baseline:
  - Bone Mineral Density (BMD) was low
  - Bone resorption biomarkers were increased

➢ Intervention: Given **Vitamin D** along with calcium
  ➢ Markers of bone resorption decreased
  ➢ BMD improved in 66% by DEXA in 22/33 boys

✧ Conclusion:
**Vitamin D is an effective first line approach in controlling bone turnover and increasing Bone Mineral Density in boys with DMD**

Guidelines for Bone Health exist in Duchenne Muscular Dystrophy


Diagnosis and management of Duchenne muscular dystrophy

<table>
<thead>
<tr>
<th>Bone-health issues</th>
<th>Recommended bone-health assessments</th>
<th>Possible bone-health interventions</th>
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</thead>
<tbody>
<tr>
<td><strong>Underlying factors for poor bone health</strong></td>
<td><strong>Suggested tests</strong></td>
<td><strong>Possible interventions</strong></td>
</tr>
<tr>
<td>Decreased mobility</td>
<td>Serum: • Calcium • Phosphate • Alkaline phosphatase • 25-OH vitamin D level (in springtime or bi-annually) • Consider: magnesium, PTH level</td>
<td>Vitamin D: • Vitamin D treatment for proven deficiency is necessary • Supplementation should be considered in all children if levels cannot be maintained</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Urine: • Calcium (for calciuria) • Sodium • Creatinine</td>
<td>Calcium: • Calcium intake and possible supplementation should be carried out in consultation with a dietitian</td>
</tr>
</tbody>
</table>

**Glucocorticoid therapy**

- Resulting in:
  - Fractures (long bone and vertebral)
  - Osteopenia
  - Osteoporosis
  - Kyphoscoliosis
  - Bone pain
  - Reduced quality of life

**Bone imaging**

- DEXA scan
  - Obtain a baseline at:
    - Age 3+ years
    - Start of glucocorticoid therapy
  - Repeat annually for those at risk:
    - History of fractures
    - On chronic glucocorticoid therapy
- DEXA Z score <-2

**Spine radiograph**

- If kyphoscoliosis is noted on clinical examination therapy
- If back pain is present, to assess vertebral compression fracture

**Bone age (left wrist) radiography**

- To assess growth failure (on or off glucocorticoid therapy)

**Bisphosphonates**

- Intravenous bisphosphonates for vertebral fracture are indicated
- Oral bisphosphonates as treatment or as a prophylactic measure remain controversial
Do individuals with FSHD have an increased risk for fractures?

- As strength ↓
  risk of falls ↑

- As muscle mass ↓
  bone mineral density ↓
How can we assess for fracture risk in the FSHD community?

• At present no guidelines exist for screening bone health in FSHD

• To address this need for the FSHD community

FSHD Bone Health Study
Conceived and designed through FSHD Global Principal Investigators
  » Dr. Kathryn Wagner, USA
  » Dr. Alastair Corbett, Australia
About Us

The FSHD Global Research Foundation is an Australian not-for-profit organisation dedicated to finding a treatment and cure for Facioscapulohumeral Dystrophy (FSHD).

Grant 23: Clinical Study of Bone Health in FSHD

Research Institution: Kennedy Krieger Institute, Baltimore, MD, USA & Concord Hospital, Sydney, NSW, Australia
Principle Investigator: Dr. Kathryn Wagner & Prof. Alastair Corbett
Primary Focus: Clinical Study of Bone Health in FSHD
Type: International and Australian Research Grant collaboration
Status: Currently underway
3 studies found for: FSHD health

Modify this search | How to Use Search Results

<table>
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<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
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<tr>
<td>1</td>
<td>Recruiting</td>
<td>Bone Health in Facioscapulohumeral Muscular Dystrophy</td>
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<td><strong>Condition:</strong> Facioscapulohumeral Muscular Dystrophy</td>
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<tr>
<td></td>
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<td><strong>Intervention:</strong></td>
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<tr>
<td>2</td>
<td>Active, not recruiting</td>
<td>Study of Morphology and Functional Magnetic Resonance Imaging (MRI)</td>
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<td>Muscle Patients With Muscular Dystrophy Type FSHD Benefiting a Physical Training Introduced.</td>
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<td><strong>Conditions:</strong> Muscular Dystrophy; Facioscapulohumeral</td>
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<td><strong>Interventions:</strong> Device: MRI; Procedure: Biopsy</td>
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<td>Unknown†</td>
<td>Molecular Analysis of Patients With Neuromuscular Disease</td>
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<td><strong>Conditions:</strong> Limb-girdle Muscular Dystrophy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy</td>
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</table>
RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Protocol Title: Bone Health in Facioscapulohumeral Muscular Dystrophy: A cross-sectional study

Application No.: IRB00031738

Sponsor: FSHD Global Research Foundation

Principal Investigator: Kathryn Wagner, MD, PhD
707 North Broadway
Baltimore, MD 21205
Phone: 443-923-9525
Fax: 443-923-9515

If you are using Epic for this study, fax a copy of the signed consent form to 410-367-7382.

Patient I.D. Plate
Cross-sectional study of bone health in adults with FSHD

- Single visit
- Neurological history & exam
- Muscle strength testing & timed functions
- DEXA scan for bone mineral density and LBM
- Serum biomarkers

- Goal - 50 patients (as of this week 42 have enrolled!)
Biomarkers

FSHD Bone Study

• Bone resorption
  • C-terminal telopeptides

• Bone formation
  • Osteocalcin, bone specific alkaline phosphatase

• Other markers of bone health
  • Calcium, TSH, PTH, CPK, CRP, Vitamin D

• Allele size
FSHD: Chromosome 4q35 deletion

**Allele sizes:**
- **Normal** = > 42kb
- **Borderline** = 38 - 41kb
- **Abnormal (FSHD-associated)** = < 38kb
FSHD1 caused by deletion of D4Z4 repeat units on Chromosome 4q35

- D4Z4 unit contains copies of the DUX4 factor that controls expression of other genes
- DUX4 normally is “turned off” or not expressed
- Deletion in the D4Z4 portion → DUX4 is expressed
- Expression of DUX4 plays a causal role in FSHD skeletal muscle pathophysiology
Aims: FSHD Bone Health Study

- **Bone mineral density and Lean body mass**
  Are they reduced in FSHD?

- Do individuals with FSHD have more fractures compared to age matched controls?

- Does BMD correlate with muscle strength and timed tests?

- Do fractures or BMD correlate with **Allele size** and **Bone turnover markers**?
Ultimate GOAL of the Study

- Provide evidence for establishing medical guidelines for screening, treatment and maintaining bone health in FSHD

- Promote highest standard of care and quality of life for the FSHD community
Osteoporosis and Fractures: Steps for prevention

• Balanced diet rich in calcium and vitamin D
• Weight-bearing exercises (dance, walk, shop)
• Healthy lifestyle with no smoking or excessive alcohol intake
• Bone density testing for at risk population
• Pharmacologic Rx for low BMD when appropriate

• Resource www.nof.org
Thank you!

**PATIENTS** and their families

Members of the Center for Genetic Muscle Disorders & the Wagner lab
Prolia (Denosumab)

- Biologic from Amgen supposedly better than others because:
  - Targeted mechanism – RANKL inhibitor
    - Inhibits formation and function of osteoclasts
  - Improved dosing schedule
    - s.c. once every 6 months
  - Superior tolerability
  - Reduced fracture risk by 68%
  - Cost >$10,000/year

- August 2009 FDA panel:
  - Data from 30 clinical trials
  - Only 2 of 6 indications
    - Safety issues
Denosumab inhibits osteoclast formation.