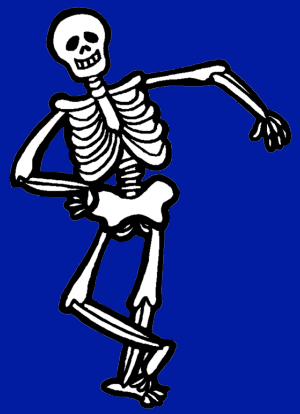
Bone Health in FSHD

June 27, 2015
Baltimore

FSH Society



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The Center for Genetic Muscle Disorders
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University of California San Diego (UCSD)
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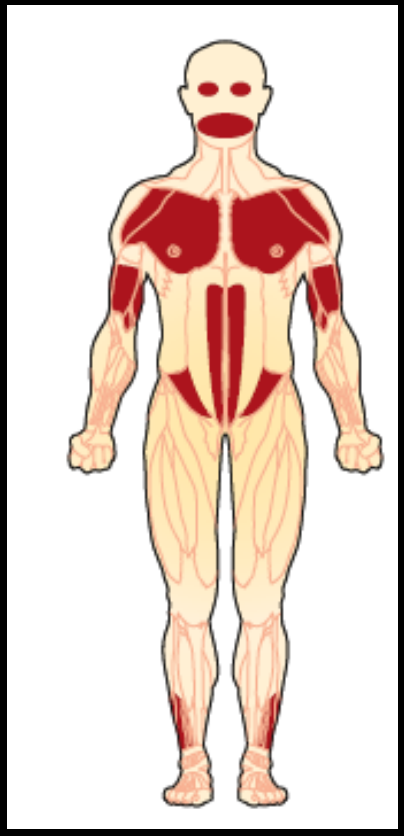
FSHD
Facioscapulohumeral Muscular Dystrophy

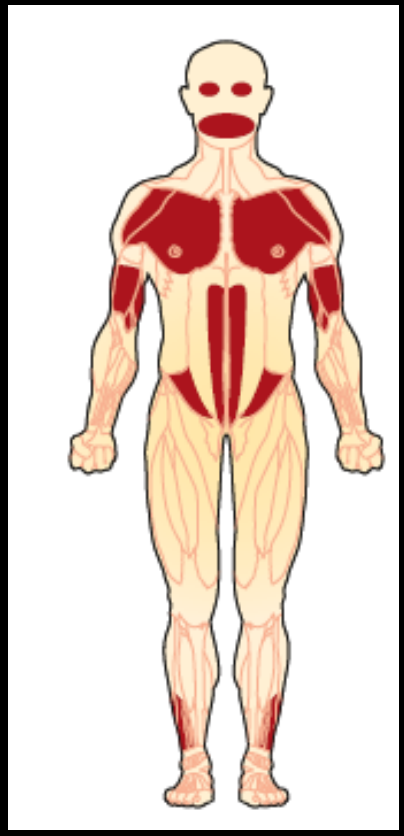
- Inherited condition
- Weakness in FSH distribution
- Loss of strength and decreased muscle mass



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

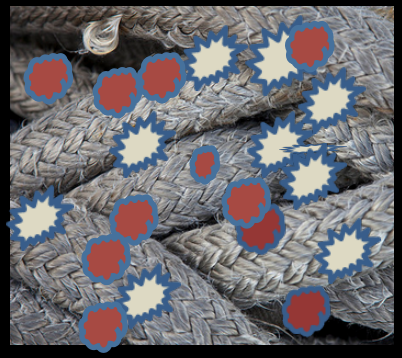
- Protects our organs from injury
- Attach to our ligaments and muscles and allows us to move

Metabolic

- Reservoir for calcium and other minerals

Components of **living** Bone

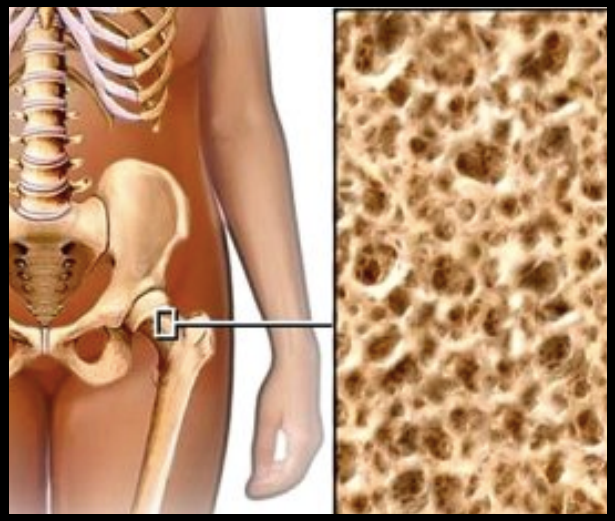
- Composed of collagen and minerals
  - Collagen is a protein that provides a flexible framework
    - Layers of twisted fibrils



  - Calcium and phosphate are minerals 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

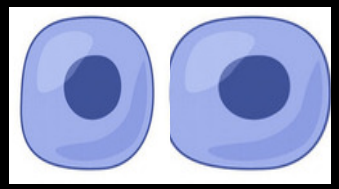
Bone Growth is Dynamic Remodeling

- 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

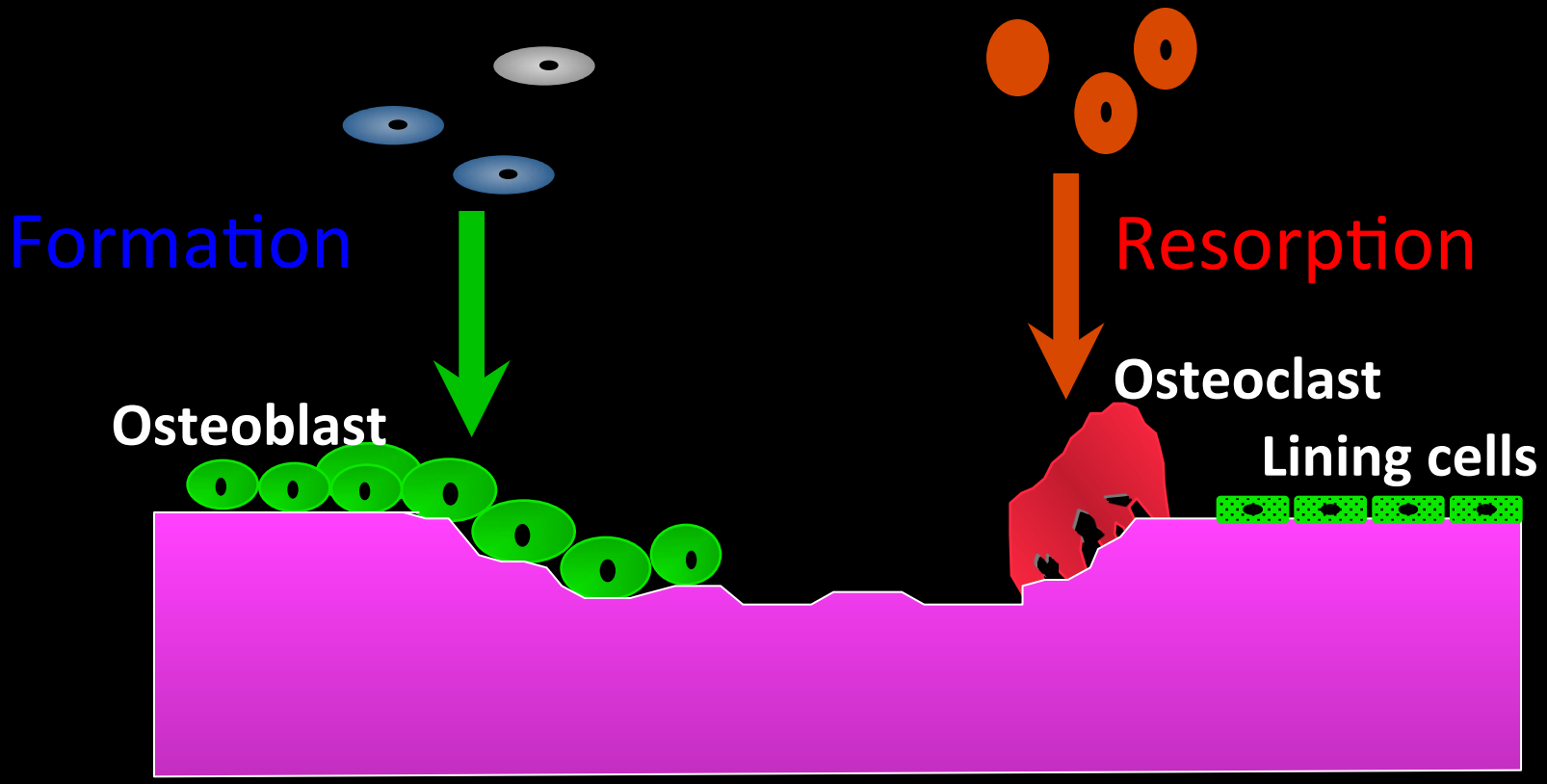
cells that lay down new bone

- Osteoclasts:

- large cells that resorb old or damaged bone

❖ Resorption breaks down and removes bone.

Bone remodeling



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

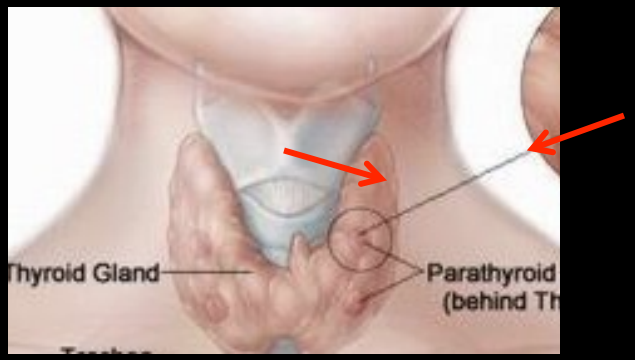
- Testosterone
  - Inhibits bone resorption and maintains bone mass
  - Low levels are associated with accelerated bone turnover and increased fracture risk

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

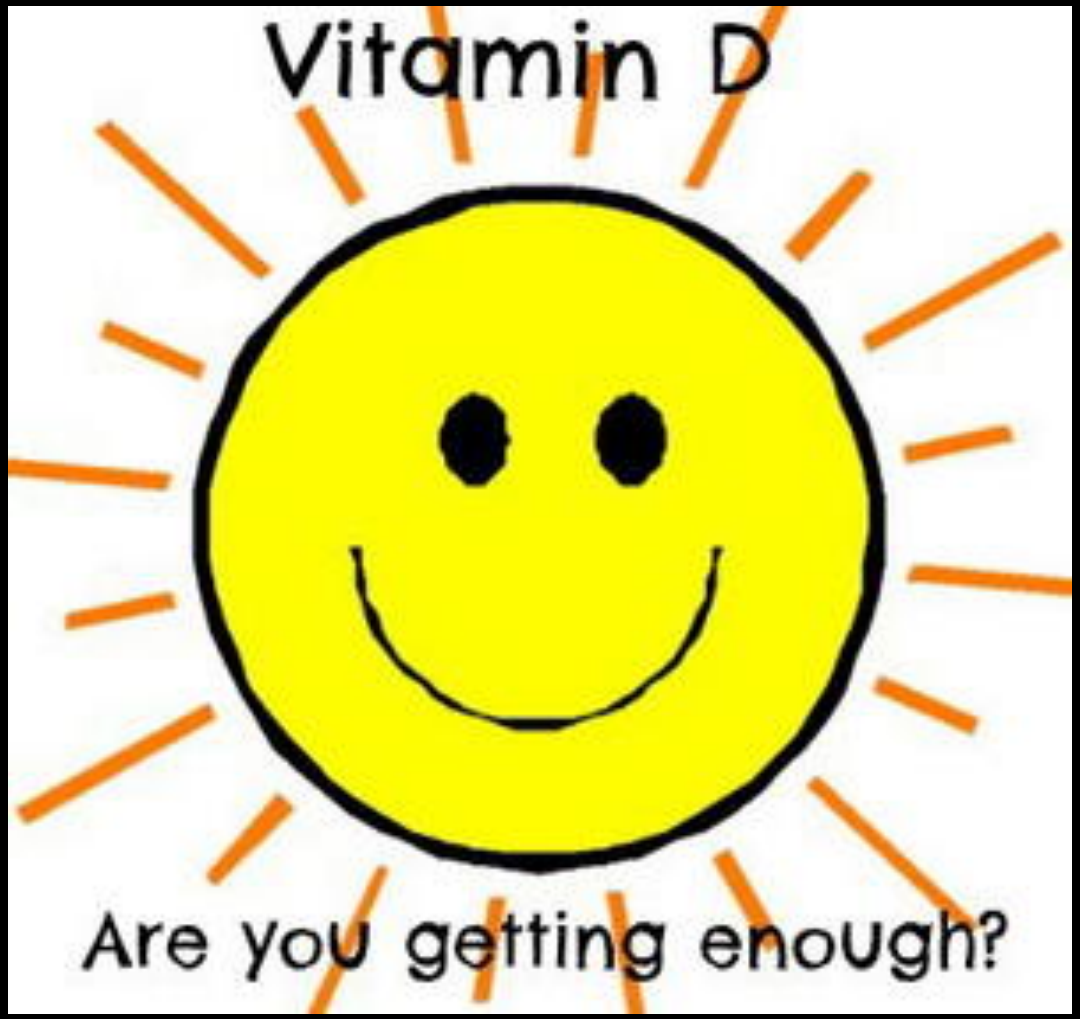
Vitamin D

- 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 D_3

- Sources?



Holick, etal

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

NIH National Institutes of Health
Office of 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

OPTIMAL DAILY CALCIUM INTAKE

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

Institute of Medicine. Calcium Dietary Reference Intakes, National Academy of Sciences, 2010.

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

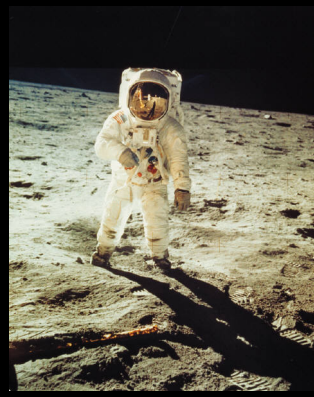
Lifestyle
Effect of Inactivity

- 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*

Keyak JH, et al. Reduction in proximal femoral strength due to long-duration spaceflight. Bone 2009;44:449-53.

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)

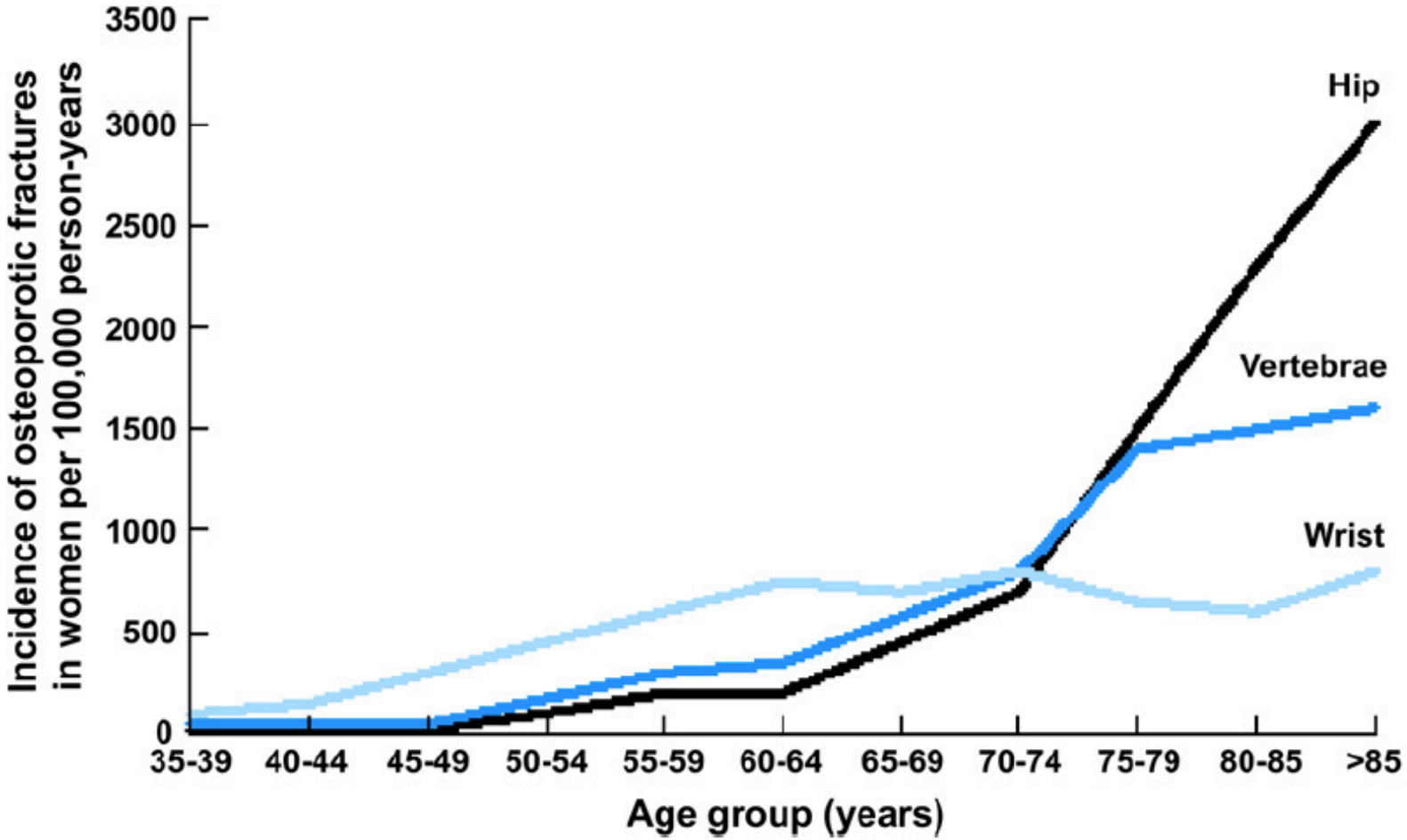
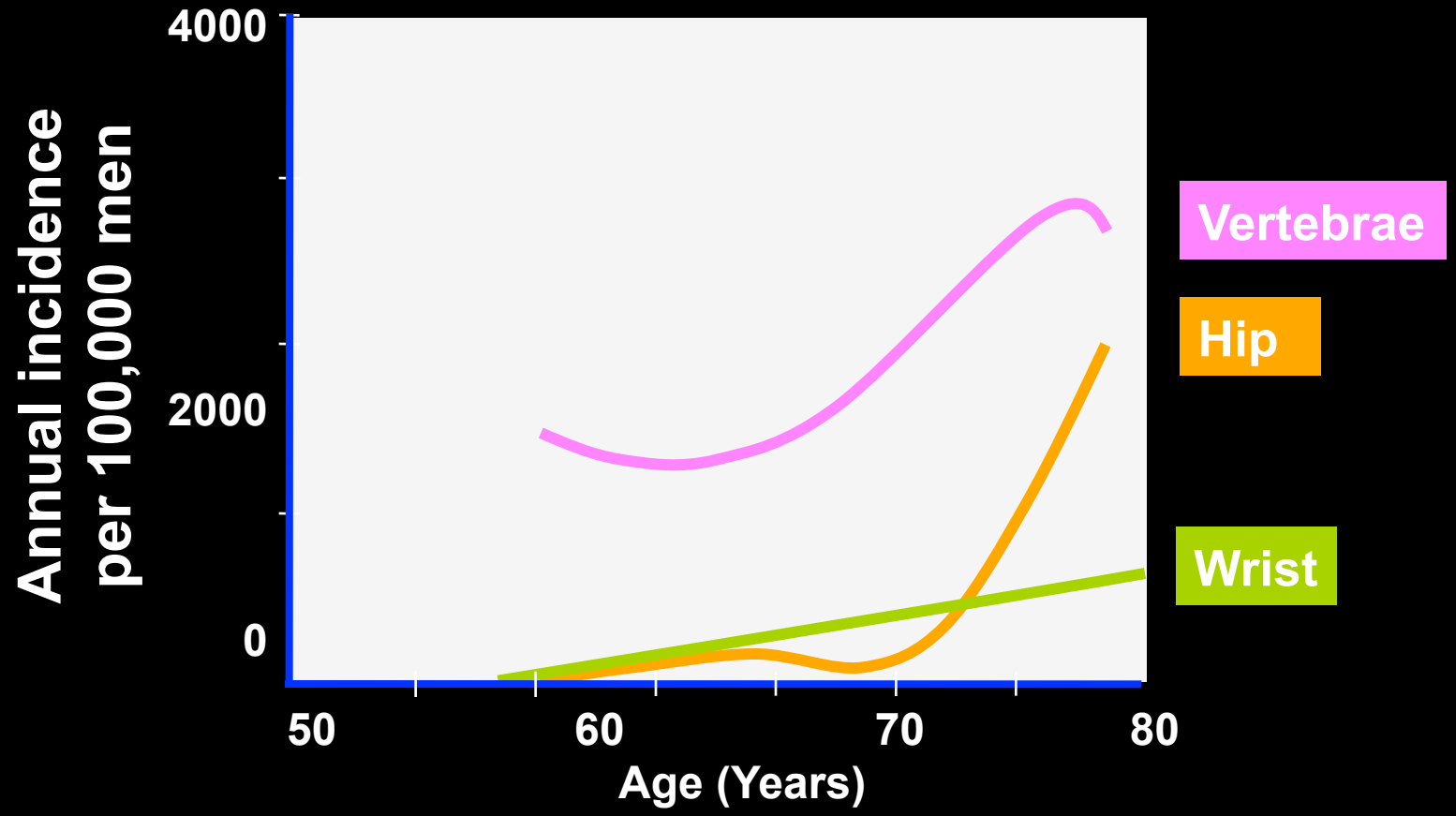


Figure 1. Incidence of osteoporotic fractures in women.

Osteoporosis: strategies for prevention Best Pract Res Clin Rheumatol. 2007 Feb;21(1):109-22. Keen R.

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?

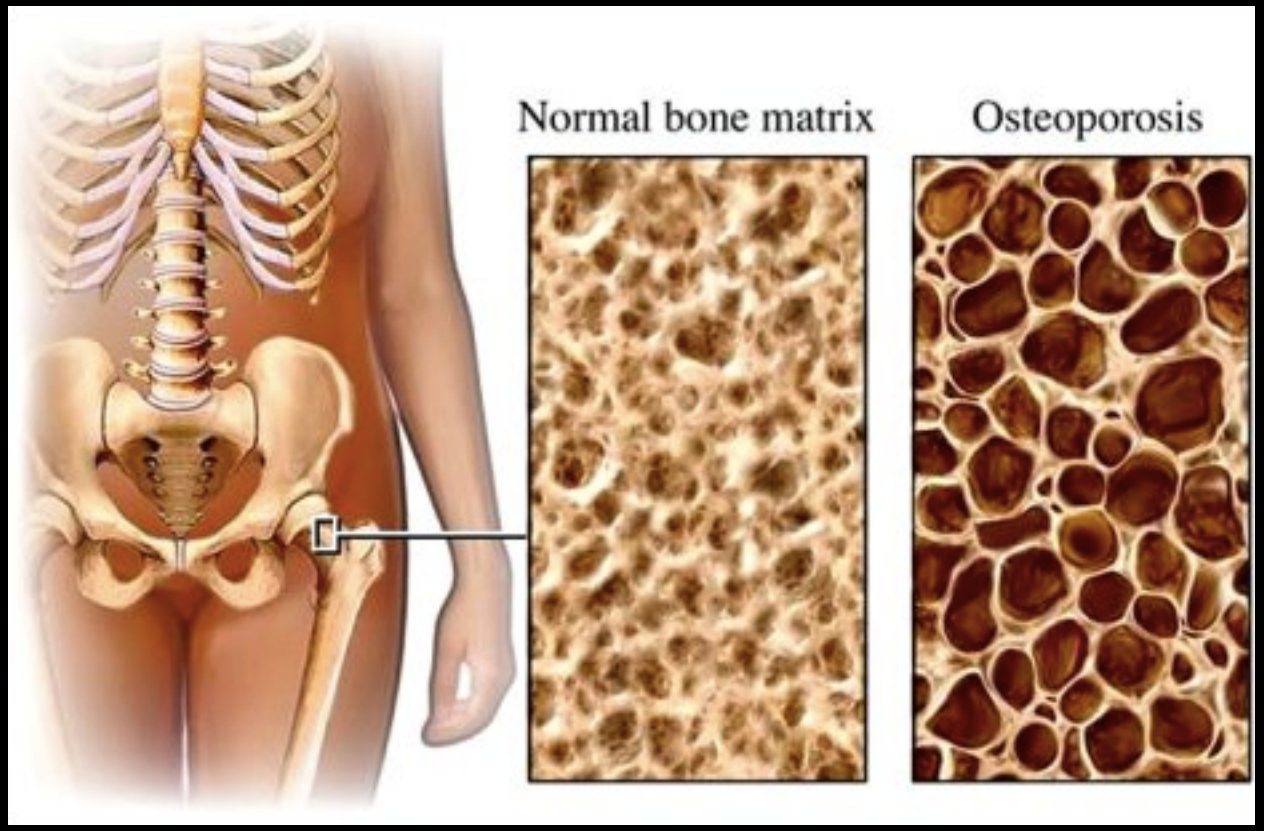
  Loss of mineral and structural integrity of the bone

- Why do we care?

  Higher risk of fractures

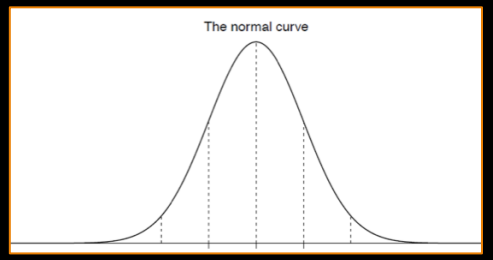
Osteoporosis

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 ≤ – 2.5 SD

- Any fragility fracture = Osteoporosis regardless of the Z score

FRAX® WHO Fracture Risk Assessment Tool

Home | Calculation Tool | Paper Charts | FAQ | References | English

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: $$$$$4$4 About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex ○ Male ○ Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture ● No ○ Yes
6. Parent Fractured Hip ● No ○ Yes
7. Current Smoking ● No ○ Yes
8. Glucocorticoids ● No ○ Yes
9. Rheumatoid arthritis ● No ○ Yes
10. Secondary osteoporosis ● No ○ Yes
11. Alcohol 3 or more units/day ● No ○ Yes
12. Femoral neck BMD (g/cm^2)

Select BMD

Clear Calculate

Print tool and information

Weight Conversion

Pounds → kg

Convert

Height Conversion

Inches → cm

Convert

03446747

Individuals with fracture risk assessed since 1st June 2011

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

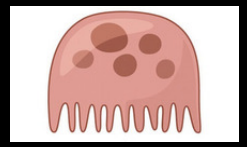
Treatment for low BMD: Bisphosphonates

- 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

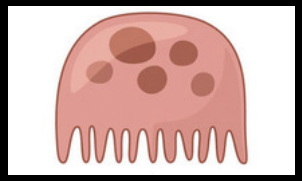


- Side effects: flu-like symptoms especially with the first infusion, hypocalcaemia and osteonecrosis of the jaw

- 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 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:

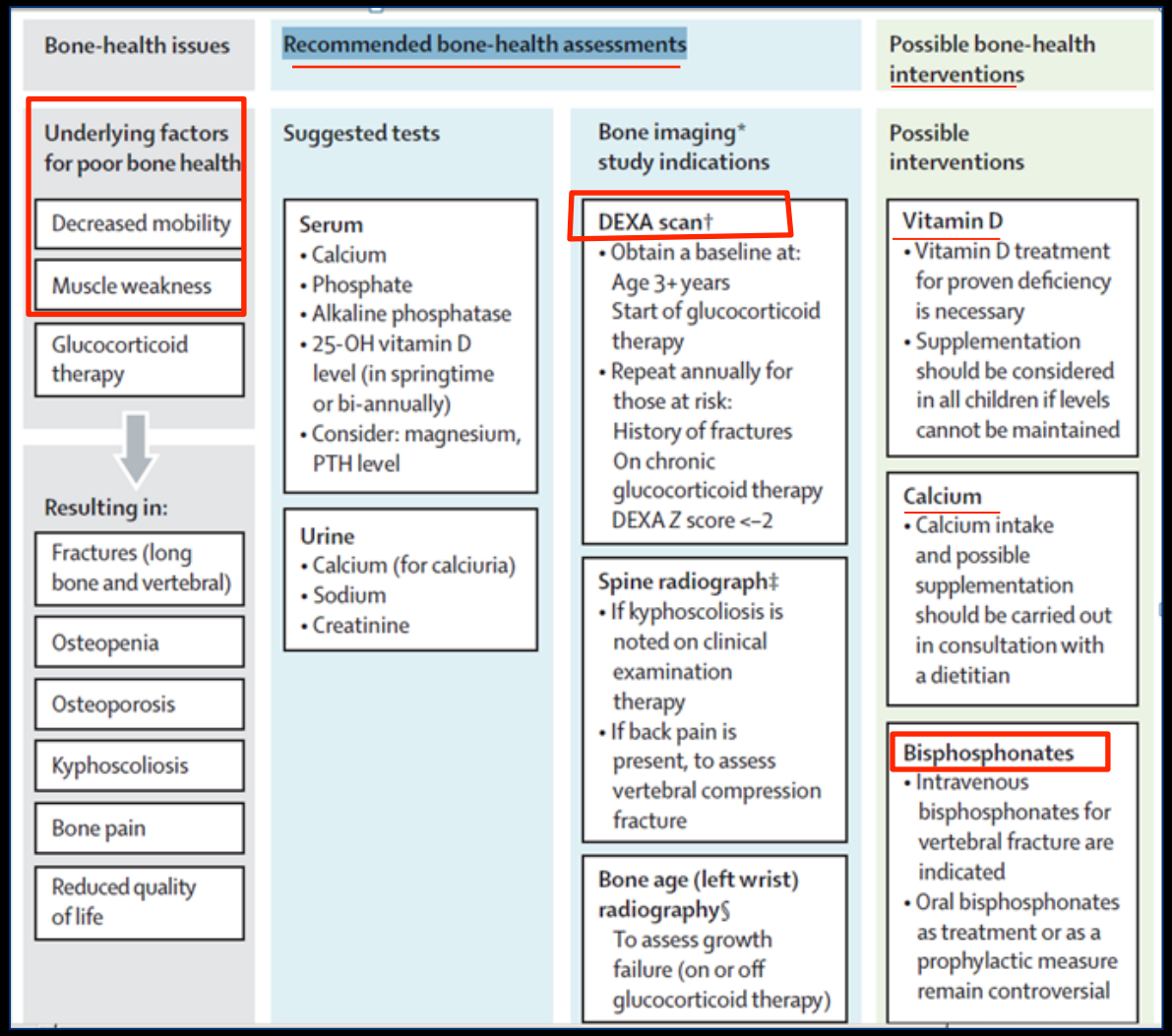
Vitamin D is an effective first line approach in controlling bone turnover and increasing Bone Mineral Density in boys with DMD

*Bianchi et al Osteoporos Int. 2011 Feb;22(2):529-39.

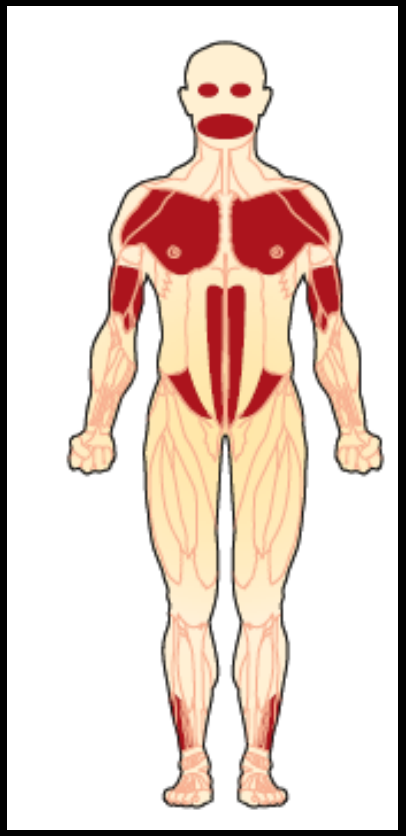
Guidelines for Bone Health exist in Duchenne Muscular Dystrophy

***From Bushby** et al: Lancet Neurol 2010; 9: 177–89.*

Diagnosis and management of Duchenne muscular dystrophy



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

FSHD

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).

FSHD research has been neglected for too long.

Help us make up for lost time.

Donate Now

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

Join our Online Community

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"

Search for studies: FSHD Search

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Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results

Text Size

3 studies found for: FSHD health

Modify this search | How to Use Search Results

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Include only open studies | Exclude studies with unknown status

Rank	Status	Study
1	Recruiting	**Bone Health in Facioscapulohumeral Muscular Dystrophy** **Condition:** Facioscapulohumeral Muscular Dystrophy **Intervention:**
2	Active, not recruiting	**Study of Morphology and Functional Magnetic Resonance Imaging (MRI) Muscle Patients With Muscular Dystrophy Type FSHD Benefiting a Physical Training Introduced.** **Conditions:** Muscular Dystrophy; Facioscapulohumeral **Interventions:** Device: MRI; Procedure: Biopsy
3	Unknown †	**Molecular Analysis of Patients With Neuromuscular Disease** **Conditions:** Limb-girdle Muscular Dystrophy; Duchenne Muscular Dystrophy; Becker Muscular Dystrophy; Facioscapulohumeral Muscular Dystrophy

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

Patient I.D. Plate

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

Cross-sectional study of bone health in adults with FSHD

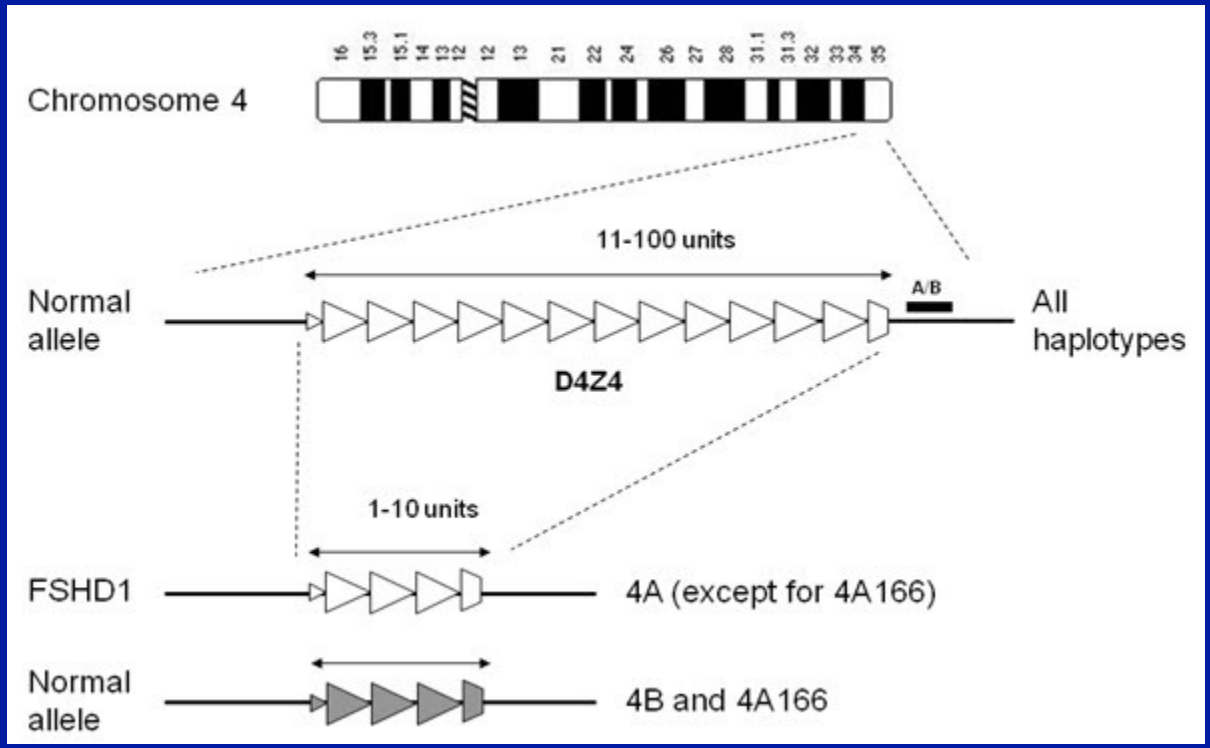
- Single visit
- Neurological history & exam
- Muscle strength testing & timed functions
- DEXA scan for bone mineral density and LBM
- Serum biomarkers

- 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

[GeneReviews]

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

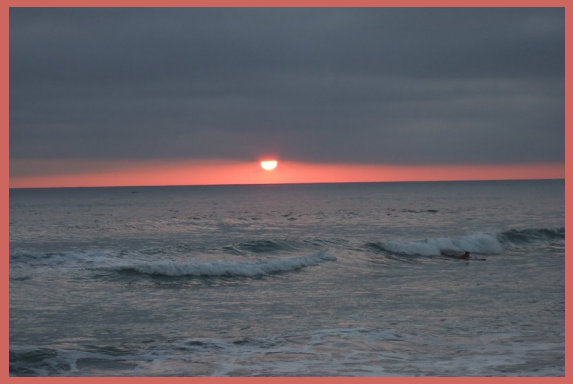
Aims:
FSHD Bone Health Study

- 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

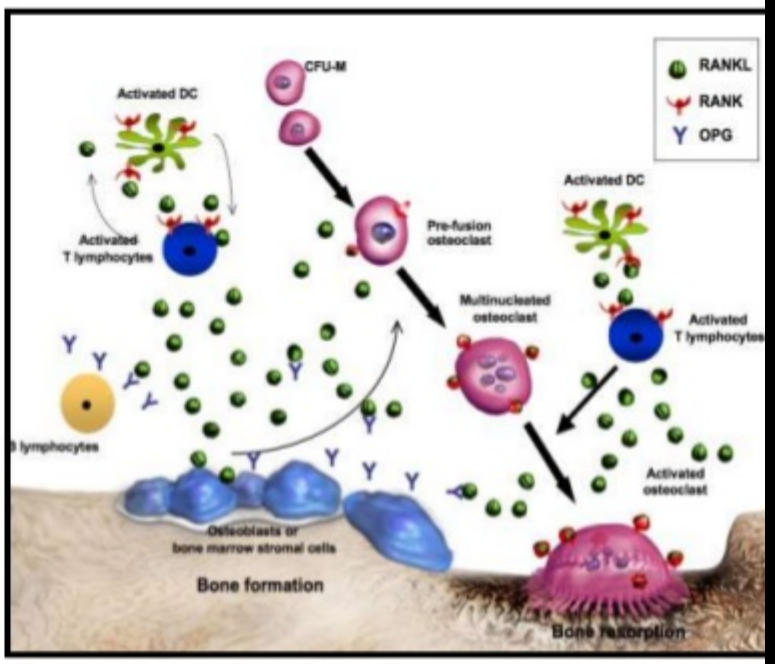
NATIONAL OSTEOPOROSIS FOUNDATION

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



RANKL denosumab inhibits osteoclast formation