Bone Health: Recurrent Fractures Recommended Evaluation and Treatment

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Objectives

- Discuss significance of trauma to fracture in regards to suspicion of underlying pathology
- Consider pubertal development in relation to fracture risk
- Review workup of child with recurrent fractures
- Discuss efficacy of various treatments to build bone strength

Disclosures

- Disclosures:
- No relevant financial relationships with any commercial interests related to this presentation.
  - 1K08AR064833 and 1R03AR073939, grant support
  - Ultragenyx Pharmaceutical Inc., grant support
  - Alexion Pharmaceuticals, grant support and prior consultant
  - Radius, Inc., consultant and grant support
- "Off-label" product use. There is no FDA-approved mediation to treat osteoporosis/skeletal fragility in children. I will however discuss the efficacy of bisphosphonate use in children, including pros and cons, as published in the medical literature and from personal experience.

Presenter: Janet L. Crane, M.D.

U.S. Department of Health and Human Services

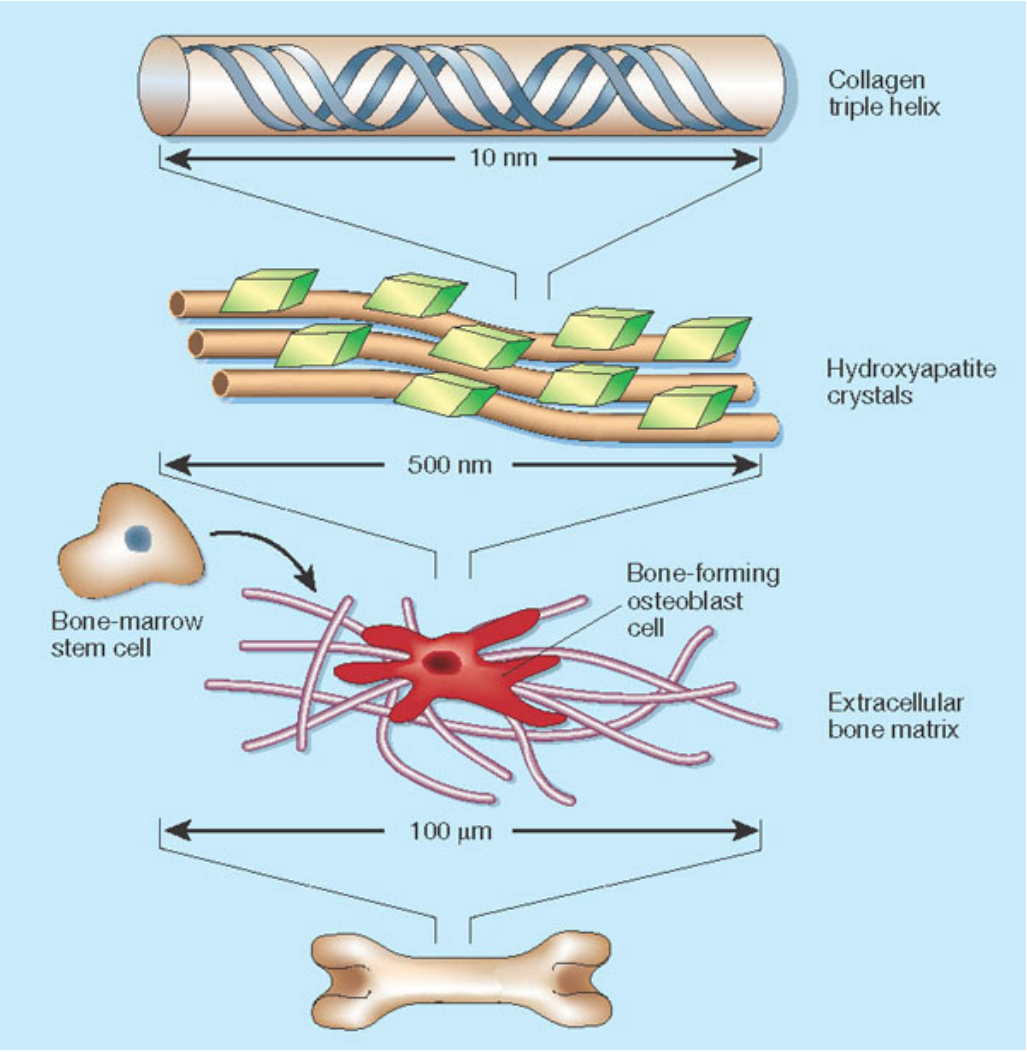
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Composition of Bone

Protein

Minerals

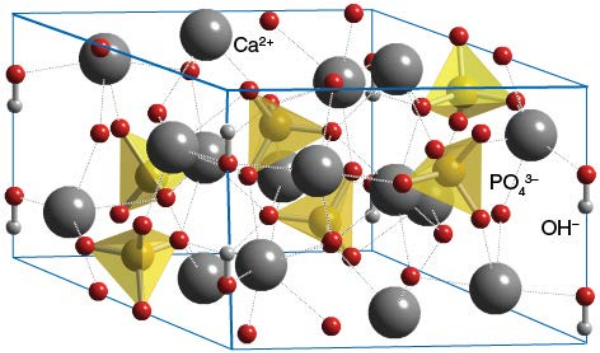
Cells

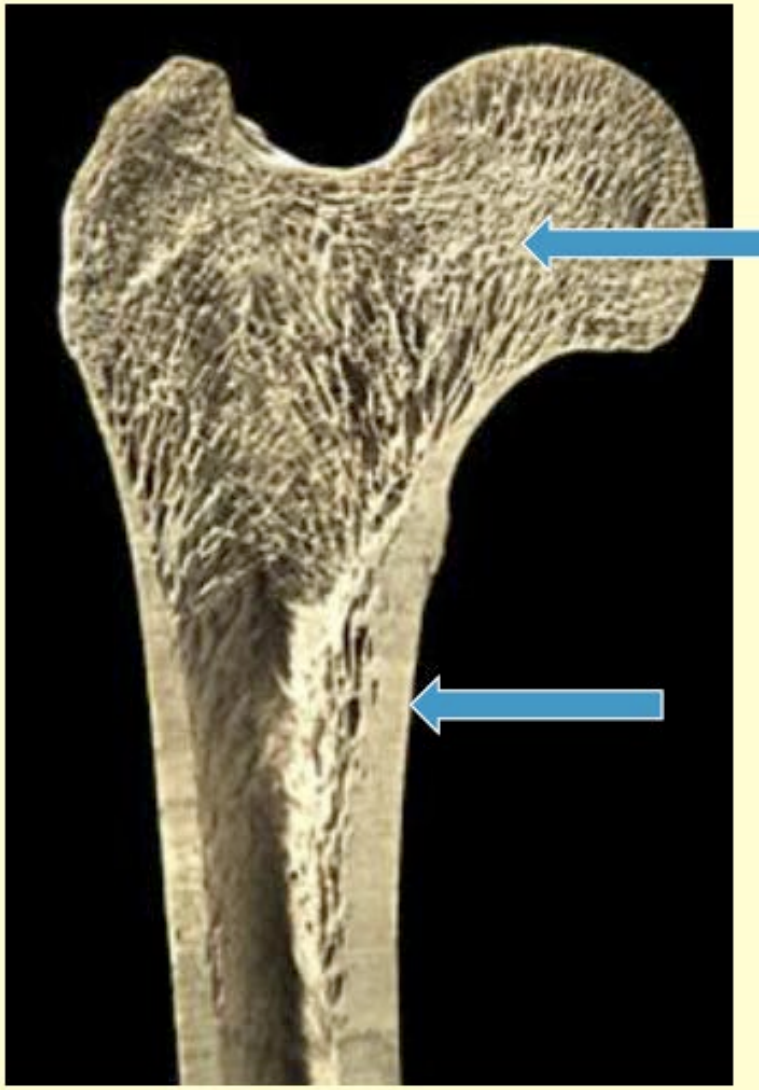


Overview of Bone

- The body contains ~1000 g of Calcium
- 99% of total body Calcium is stored as hydroxyapatite in the bone

$Ca_{10}(PO4)_6(OH)_2$

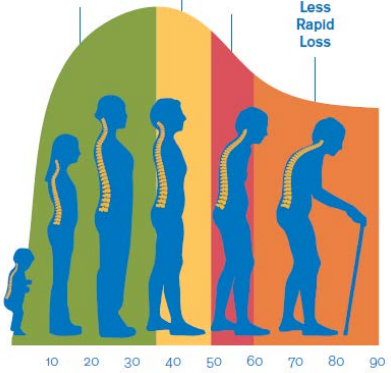


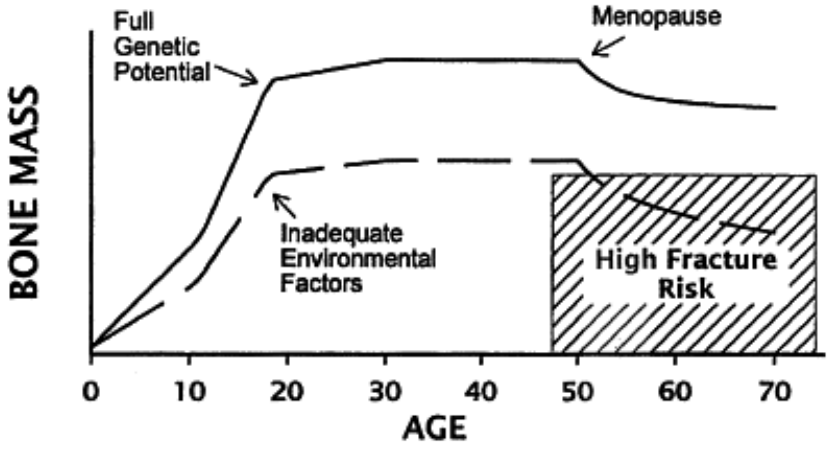


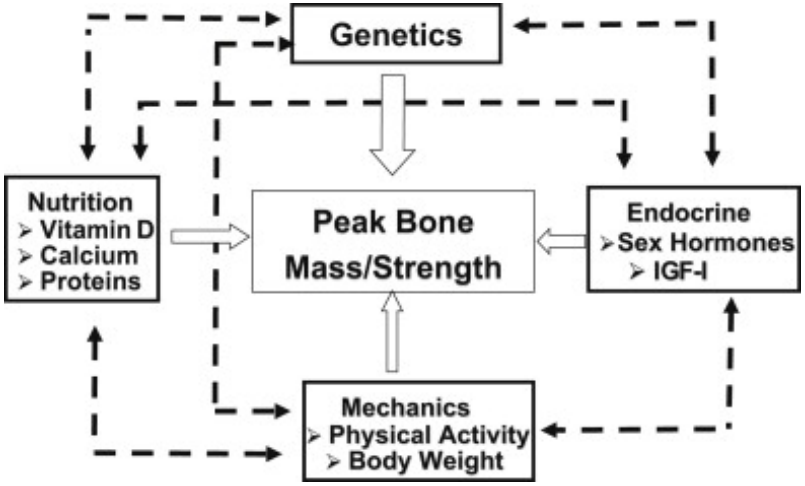
Trabecular bone
- Metabolically active
- Strength

Cortical bone
- Strength

Peak Bone Mass







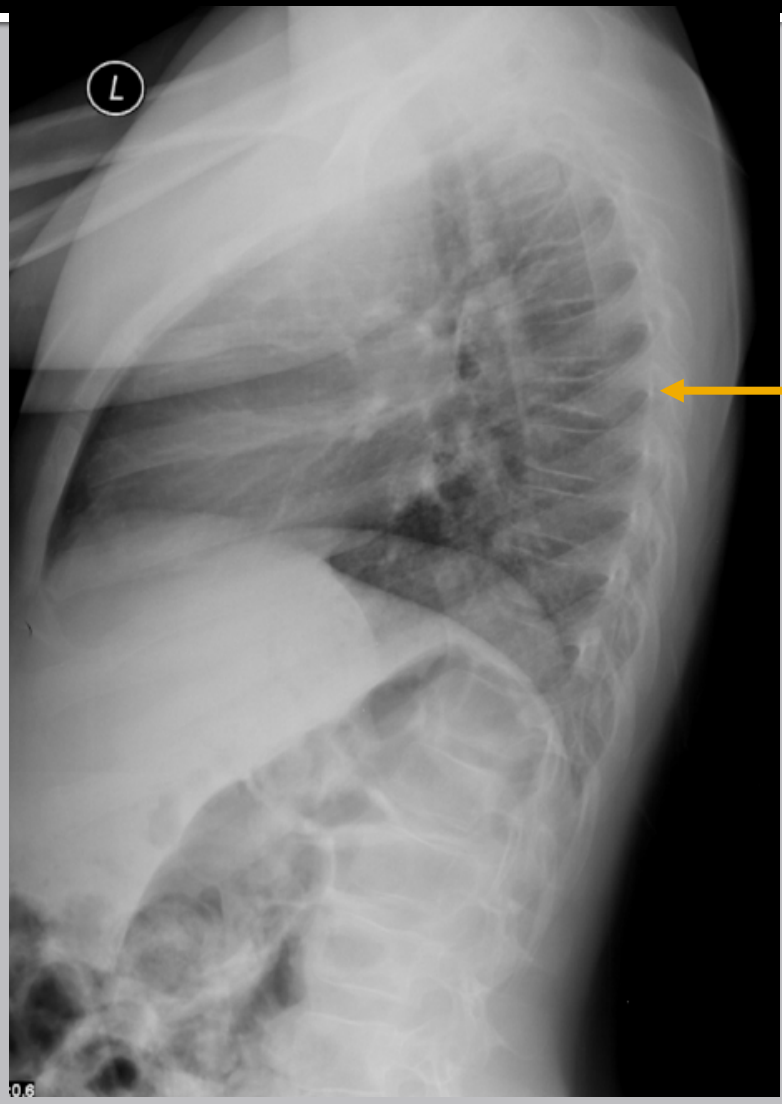
Bonjour JP, Chevalley T, Ferrari S, Rizzoli R. Peak bone mass and its regulation. Pediatric Bone: Biology and Diseases, 2nd Ed. 2012.

Goal of the body is to build only skeleton you need and maintain the integrity of it.

- Bone is metabolically active and takes a tremendous amount of energy to maintain.
- The body builds enough bone to keep the skeleton as strong as needed, but minimizes the amount of bone built to reduce unnecessary energy expenditure.
- When bone is damaged, the body repairs the damage.

Case 1

- 9.5 yo female with intermittent back pain
- HPI: Normal, healthy active kid. Intermittent back pain over past 12 months. Severe enough to restrict activities, but would resolve with rest. 5 months prior, fell down about 12 carpeted stairs. Complained of back pain again. After about 2 weeks, had x-ray of back.
- Exam: Ht 77th %ile). Wt 79th %ile). BMI 77th %ile. Normal exam. Prepubertal.

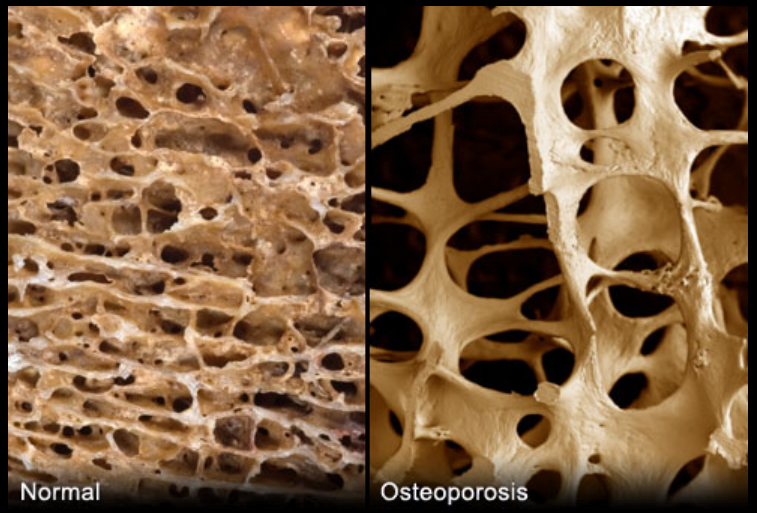


Case 2

- 14 yo male with 4th forearm fracture
  - Age 11, fx left and right radius and ulna, riding bike, pulled front bike, and flew over handle bars, closed reduction
  - Age 13, fx left radius/ulna, playing Frisbee, fell and tripped with full force onto left arm, closed reduction
  - Age 13 (3 months later), fx left radius/ulna, on canoeing trip with friends, chest bumped friend and fell backwards, using arm to brace his fall, open reduction, internal fixation
  - Age 14, buckle fx right wrist, fell backwards from standing, landing on outstretched arm, casted

Case 3

- 17 yo female, four stress fracture/reactions in 2 years (metatarsal, tibia), elite cross country athlete
- History of anorexia at 12 years of age, lasted 1.5 years, lowest BMI was 15.2 kg/m2 (4^{th}%ile, z score -1.74), BMI now at 54-64rd % ile).
- Primary amenorrhea – menses only with estradiol 75 mcg patch and provera challenge



Which (if any) case has osteoporosis?

Definition of Osteoporosis

- The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis, in the absence of local disease or high-energy trauma.
- In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of both a clinically significant fracture history and BMD Z-score ≤ -2, adjusted for age, gender, and body size as appropriate.
- A clinically significant fracture history is one or more of the following:
  - Two or more long bone fractures by age 10 yr;
  - Three or more long bone fractures at any age up to 16 yr.
  - Vertebral compression fracture (loss of 20% height at any point).
  - *Fracture secondary to mild trauma*
- A BMD/BMC Z-score ≥ -2.0 does not preclude the possibility of skeletal fragility and increased fracture risk.
- The diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of densitometric criteria alone.

Bishop N, Arundel P, Clark E, Dimitri P, Farr J, Jones G, Makitie O, Munns CF, Shaw N. Fracutre prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 pediatric official positions. J Clin Densit. 2014 http://dx.doi.org/10.1016/j.jocd.2014.01.004

Kids are clumsy (and crazy). Fractures may be a normal part of childhood

When is a fracture pathologic?

Fracture Incidence Throughout Life

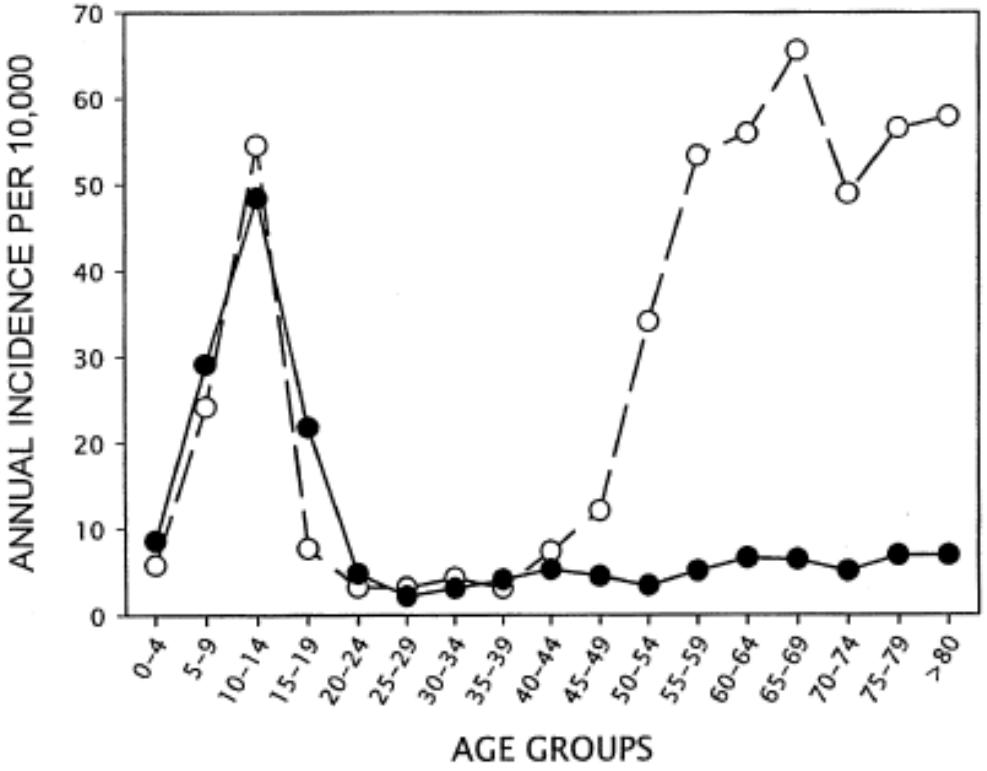
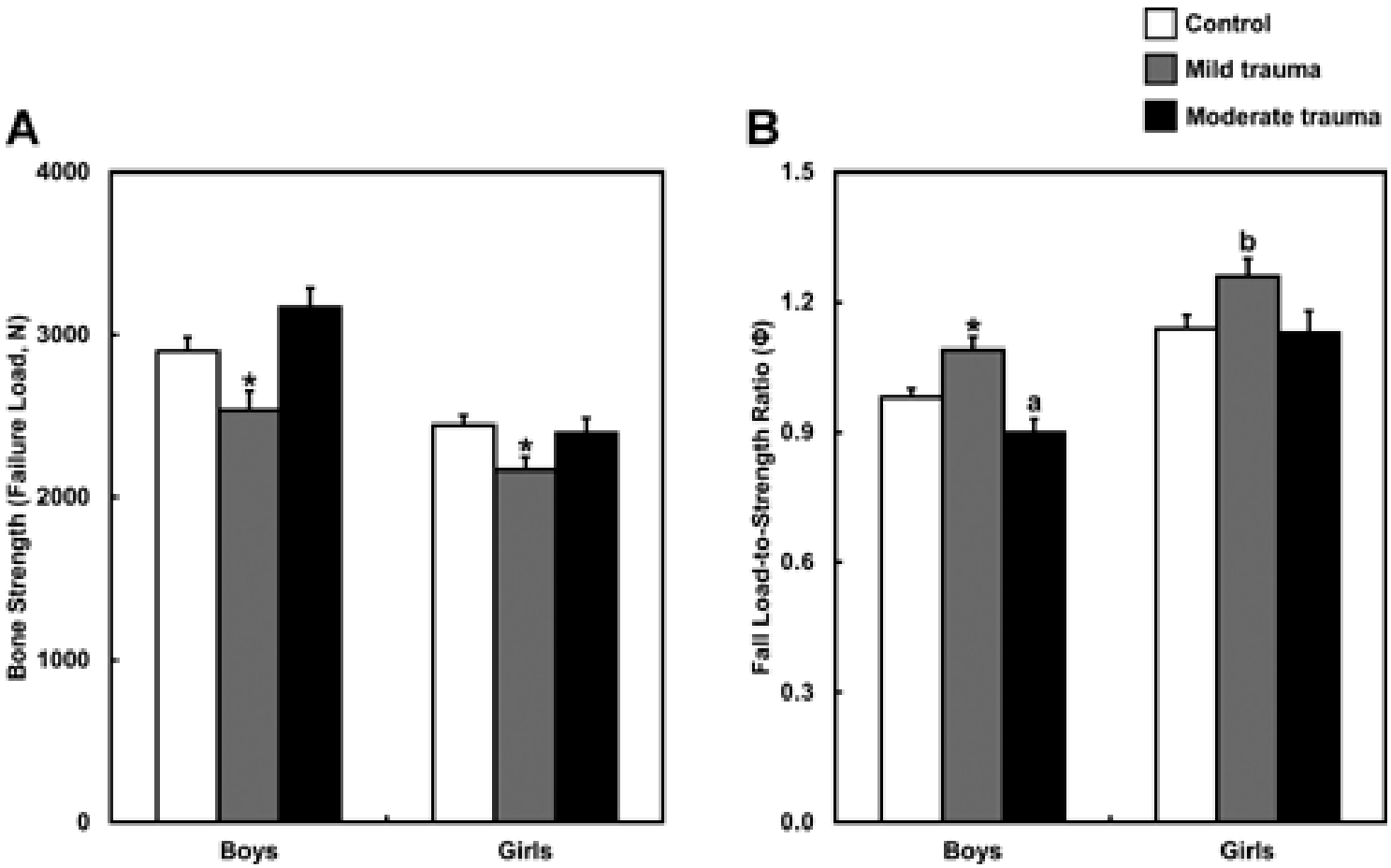


Fig. 2. Age-specific incidence of limb fractures in males (*filled circles*) and females (*open circles*) from Southern Sweden. (Adapted from Alffram and Bauer [17], with permission.)

Bone Strength in Children and Adolescents With a Distal Forearm Stratified by Trauma



Journal of Bone and Mineral Research
Volume 29, Issue 3, pages 590-599, 19 FEB 2014 DOI: 10.1002/jbmr.2071
http://onlinelibrary.wiley.com/doi/10.1002/jbmr.2071/full#jbmr2071-fig-0001

Trauma based fractures

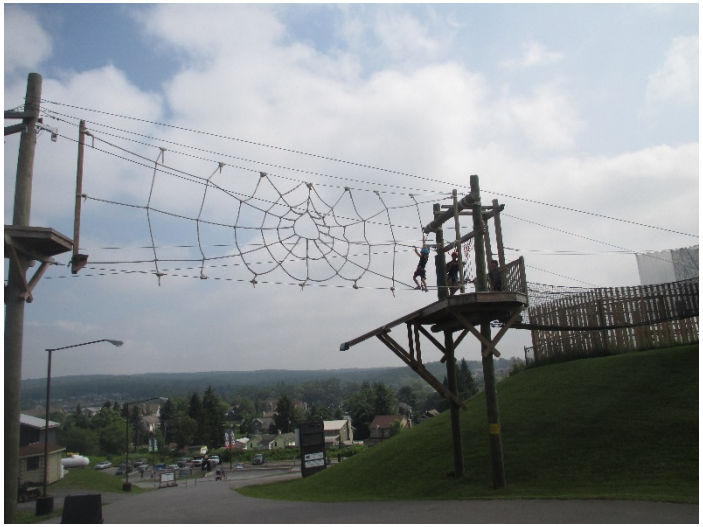
Mild Trauma

Table 1. Descriptive Categories of Landin's Modified Trauma Levels[a]

Descriptives indicating mild trauma
Falling onto the ground from standing height or less (<0.5 m)
Falling onto a resilient surface (eg, rubber, grass, or sand) from 0.5 m to 3 m
Falling from a bed or couch
Playing injuries including playground scuffles
Falling while moving at slow speed on a scooter, skateboard, skis, rollerblades, or skates
Lower-energy collisions with an object moving at slow speed
Lower-energy sport injuries (eg, basketball and soccer)

Trauma based fractures

Moderate to Severe Trauma



Descriptives indicating moderate trauma

- Falling onto concrete or other nonresilient surface from 0.5 m to 3 m
- Falling onto another person resulting in a moderate-energy collision
- Falling from a bunk bed
- Falling down stairs
- Falling from a bicycle or horseback
- Falling from a swing or slide or similar playground equipment
- Falling while moving at fast speed on a scooter, skateboard, skis, rollerblades, or skates
- Moderate-energy collisions with an object moving at fast speed
- Moderate-energy collisions between two moving objects (eg, football and hockey)

Descriptives indicating severe trauma

- Falling from a height exceeding 3 m (~10 feet)
- Traffic accidents
- Being hit by a moving heavy object

[a]Adapted from Clark and colleagues.[11]

Stress Fractures

	Fatigue fractures	Insufficiency fractures
Definition	Fracture resulting from abnormal chronic repetitive stress on normal bone	Fracture secondary to normal stress on abnormally weakened bone
Epidemiology	Young, athletes Females > males	Elderly Low body mass index (BMI) Females > males
Pathophysiology	Abnormal load leads to remodeling; when resorption is greater than replacement a fracture occurs	Normal load on weakened bone (osteopenia or metabolic bone disease)
Common locations	Tibia, fibula, metatarsals, femoral neck, pubic rami, calcaneus, and navicular	Sacrum, pubic rami, superior acetabulum, femoral head, medial femoral condyle

(Emergency Radiology 2016; 23 (4): 365–375)

Fatigue Fractures

EXTRINSIC FACTORS

- Training regimen
- Footwear
- Training surface
- Type of sport
  - Sprinters, hurdlers, and jumpers → foot fractures
  - Long distance runners → long bone and pelvic fractures

Treat with modifications to activity and address intrinsic factors

INTRINSIC FACTORS

- Gender, age, race
- Overall fitness level
- Skeletal, muscle, joint, and biomechanical factors
- Malalignments
  - hyper/hypo-pronation
  - Pes planus/cavus
  - Forefoot or hindfoot varus/valgus,
  - Tibia vara
  - Genu valgum/varum,
- Limb length discrepancies
- Tarsal coalition
- Previous surgeries or trauma to the same or opposite limb
- Joint laxity or instability
- Muscles weakness or imbalance

(Emergency Radiology 2016; 23 (4): 365–375)

Insufficiency Fractures

- Predisposing factors have been identified as the cause of insufficiency fractures with the common entity often being osteoporosis (primary or secondary)
- Evaluate for underlying chronic medical disorder: rheumatoid arthritis, metabolic bone disease, neurological disorders, prior irradiation, corticosteroid therapy, high-dose fluoride therapy
- Location of fracture may help discern fatigue versus insufficiency
  - Spine (vertebral compression fractures)
  - Sacrum or pelvis
  - Lateral femoral neck, or
  - Subchondral regions of the femoral head or medial femoral condyle of the knee.
- Treatment: address underlying chronic disease, optimize pubertal hormones, consider bisphosphonates

(Emergency Radiology 2016; 23 (4): 365–375)

Assessment

Who should be assessed? What should be included in the assessment?

Who should be assessed?

- Clinical Judgment Required (information gained during history)
  - Disease severity
  - Number of fractures
  - Nature of trauma

  - Is work-up feasible?
  - Will results change management?

Bone Health Screen

- Review diet, activity, medications, fractures, family history of fractures, pubertal timing
- Physical exam: height, weight, BMI, spine, extremities (shape, range of motion, strength), pubertal Tanner stage
- Labs
  - Calcium, phosphorus, alkaline phosphatase, magnesium
  - Vitamin D (25-OH and 1,25-dihydroxy-Vitamin D)
  - Intact PTH
  - Urine calcium/creatinine ratio
  - Urine phosphate
  - Celiac screen
  - Thyroid functions tests

When to order a DXA?

- Chronic illness associated with low bone mass
  - Specific recommendations for CF and childhood cancer
  - Celiac- one year after diagnosis if not compliant with GFD
  - Clinical judgment
    - Disease severity
    - Exposure to potentially harmful medications
    - Bone pain (especially back pain)
    - Spinal deformity
- Immobilization
- Osteopenia noted on plain film
- Recurrent fractures
- Low impact fracture
  - Fracture occurring from standing height or less

DXA caveats

- Should be done by a certified bone densitometry technologist, preferably one trained in pediatric bone densitometry
- Interpreted by z-score, adjusted for age and height

- If done on Hologic, can interpret at: https://bmdcs.nichd.nih.gov/

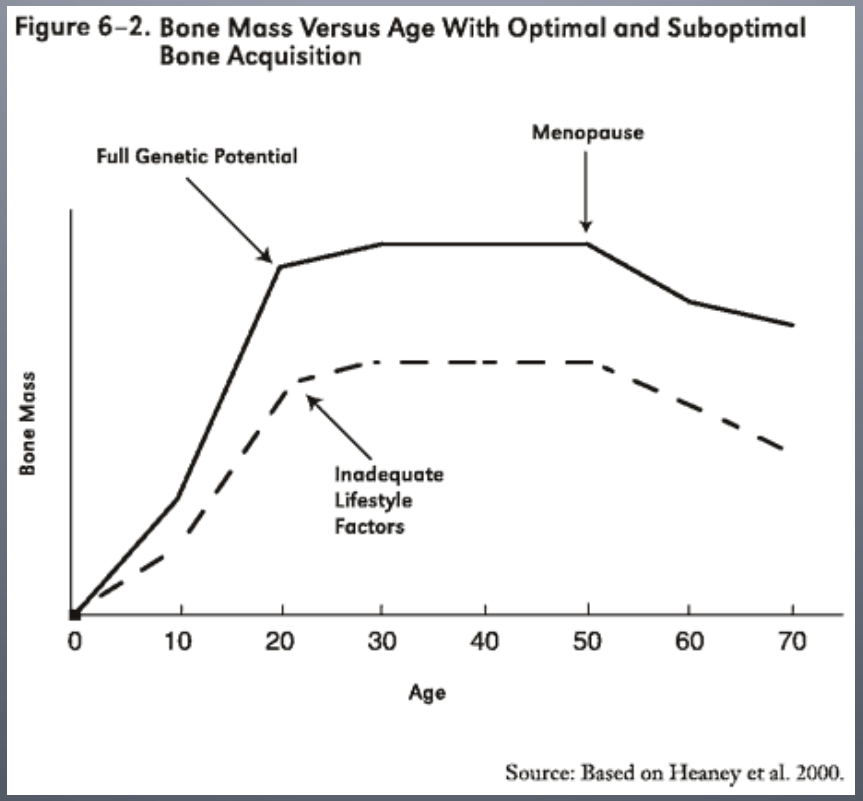
Treatments

Do they really work? What is the evidence?

Treatment strategies in children

- Reduce/limit modifiable skeletal risk factors
  - Calcium, vitamin D, and protein intake
  - Optimize weight
  - Optimize pubertal status
  - Improve control of underlying disease
  - Limit osteotoxic agents
  - Increase skeletal loading
- Pharmacological therapy

Genetic potential can only be reached if nutrition, activity, and hormone production are adequate in the first 2 decades of life



Genetics determines 60-80% of bone mass/strength

Bachrach LK 2007 Endocr Pract 13(5):513-20

BMD and vitamin D

- Supplementation with vitamin D if 25-OH vitamin D < 15 ng/ml shows some (mild) improvement in bone
  - Lumbar BMD ↑ 1.7%
  - Total body BMC ↑ 2.6%
- No changes when 25OH vitamin D > 15 ng/ml

Winzenberg, Powell Shaw, Jones. BMJ. 2011 Jan 25;342:c7254. doi: 10.1136/bmj.c7254.

Exercise and Bone

- BMD is positively correlated with childhood activity
- Intervention studies have shown improvement in bone mass and size with exercise in children
- Long-term tennis players have 10-35% greater cortical thickness and higher bone mass in the playing versus non-playing arm
- Greatest increase in BMD when started before puberty and around the time of puberty

Lofgren B et al 2011 JBMR

ORIGINAL ARTICLE

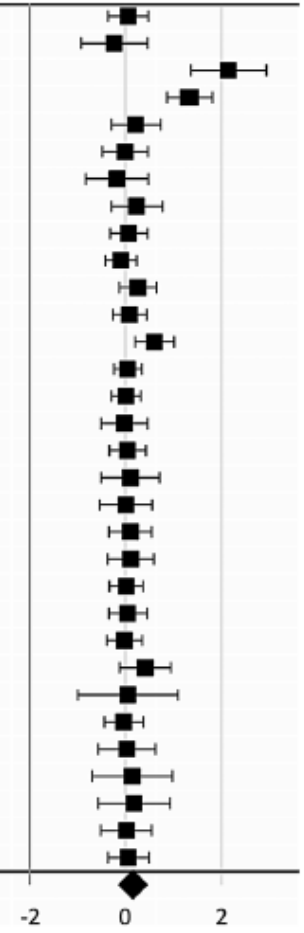
JBMR®

Effects of Weight-Bearing Activities on Bone Mineral Content and Density in Children and Adolescents: A Meta-Analysis

Michael Behringer, Sebastian Gruetzner, Molly McCourt, and Joachim Mester

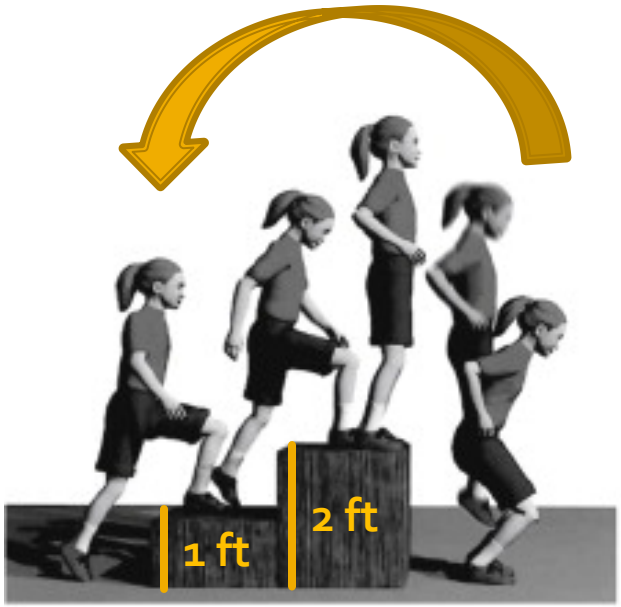
Institute of Training Science and Sport Informatics, German Sport University Cologne, Cologne, Germany

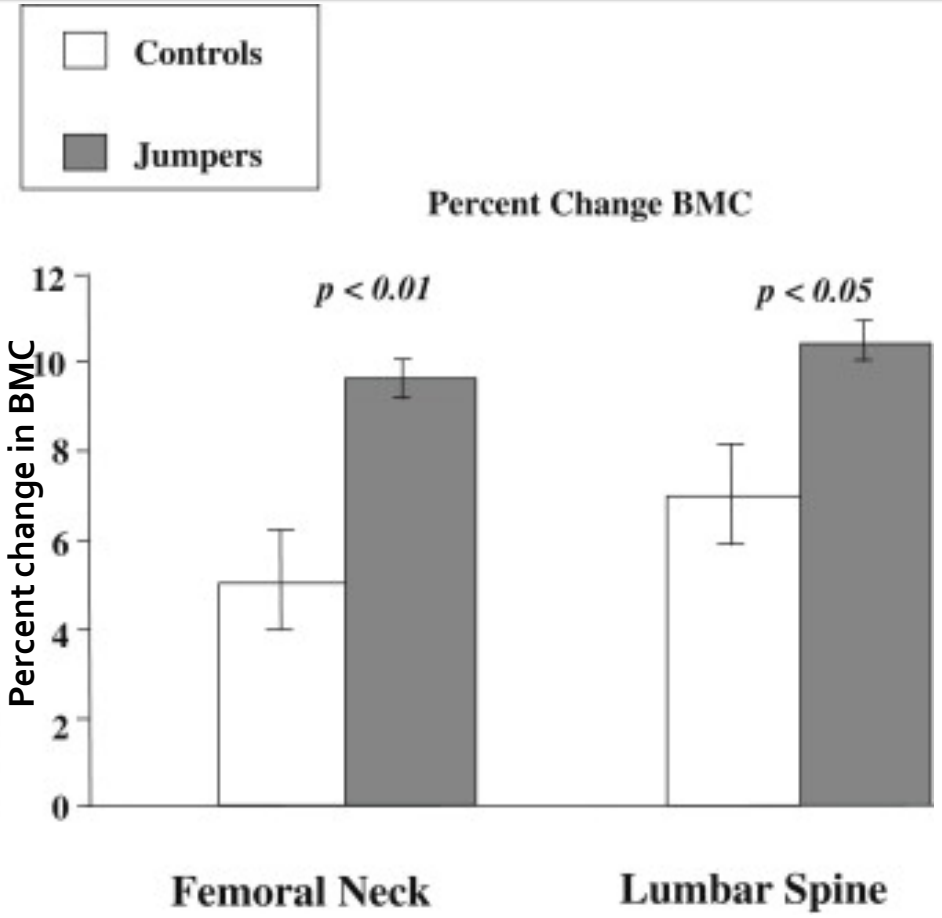
Study	Subgroup	ES	Var	SE	Lower limit	Upper limit	Z value	p	Relative Weight
Bianchini et al., 2012		0.07	0.05	0.22	-0.35	0.49	0.33	0.74	9.39
Blimkie et al., 1996		-0.22	0.13	0.36	-0.92	0.48	-0.62	0.54	5.37
Bradney et al., 1998		2.15	0.17	0.41	1.35	2.95	5.27	0.00	4.43
Fuchs et al., 2001		1.35	0.06	0.23	0.89	1.81	5.74	0.00	8.69
Heinonen et al., 2000	Premenarcheal	0.23	0.07	0.27	-0.29	0.75	0.86	0.39	7.65
Heinonen et al., 2000	Postmenarcheal	0.01	0.06	0.25	-0.48	0.49	0.02	0.98	8.33
Iuliano-Burns et al., 2003		-0.17	0.11	0.34	-0.83	0.49	-0.49	0.62	5.75
Johannsen et al., 2003		0.25	0.08	0.28	-0.29	0.79	0.91	0.36	7.34
Kontulainen et al., 2002		0.08	0.04	0.20	-0.31	0.48	0.40	0.69	9.96
Laing et al., 2005		-0.08	0.03	0.17	-0.41	0.25	-0.49	0.63	11.34
Linden et al., 2006		0.28	0.04	0.20	-0.12	0.67	1.37	0.17	9.93
Löfgren et al., 2012	Male	0.10	0.03	0.18	-0.25	0.46	0.56	0.58	10.75
Löfgren et al., 2012	Female	0.62	0.04	0.21	0.21	1.04	2.97	0.00	9.61
Macdonald et al., 2008	Male	0.06	0.02	0.15	-0.23	0.36	0.41	0.68	12.09
Macdonald et al., 2008	Female	0.02	0.03	0.16	-0.29	0.33	0.13	0.90	11.74
MacKelvie et al., 2001	Prepubertal	-0.01	0.06	0.25	-0.50	0.47	-0.04	0.97	8.25
Mackelvie et al., 2001	Early Pubertal	0.05	0.04	0.20	-0.33	0.44	0.27	0.79	10.12
MacKelvie et al., 2002	Asian	0.12	0.10	0.31	-0.50	0.73	0.37	0.71	6.32
MacKelvie et al., 2002	White	0.02	0.08	0.28	-0.53	0.58	0.09	0.93	7.14
MacKelvie et al. ,2003		0.11	0.05	0.23	-0.34	0.57	0.50	0.62	8.79
MacKelvie et al., 2004		0.12	0.06	0.25	-0.37	0.61	0.49	0.62	8.15
McKay et al., 2005		0.03	0.03	0.18	-0.33	0.39	0.16	0.88	10.72
Meyer et al., 2011	Prepubertal	0.06	0.04	0.21	-0.34	0.47	0.31	0.76	9.78
Meyer et al., 2011	Early Pubertal	-0.01	0.04	0.19	-0.39	0.37	-0.05	0.96	10.33
Morris et al., 1997		0.43	0.08	0.28	-0.11	0.97	1.56	0.12	7.31
Nichols et al., 2001		0.07	0.29	0.54	-0.99	1.12	0.12	0.90	2.85
Specker and Binkley, 2003		-0.02	0.04	0.21	-0.44	0.39	-0.10	0.92	9.58
Van Langendonck et al., 2003		0.04	0.10	0.31	-0.56	0.65	0.14	0.89	6.44
Weeks et al., 2008	Male	0.16	0.19	0.43	-0.69	1.01	0.36	0.72	4.03
Weeks et al., 2008	Female	0.20	0.15	0.39	-0.56	0.95	0.50	0.61	4.76
Witzke et al., 2000		0.03	0.08	0.28	-0.51	0.57	0.12	0.90	7.37
Yu et al., 2005		0.08	0.05	0.22	-0.36	0.51	0.35	0.73	9.19
Total (Random)		0.17	0.00	0.06	0.05	0.29	2.72	0.01	



Physical Activity

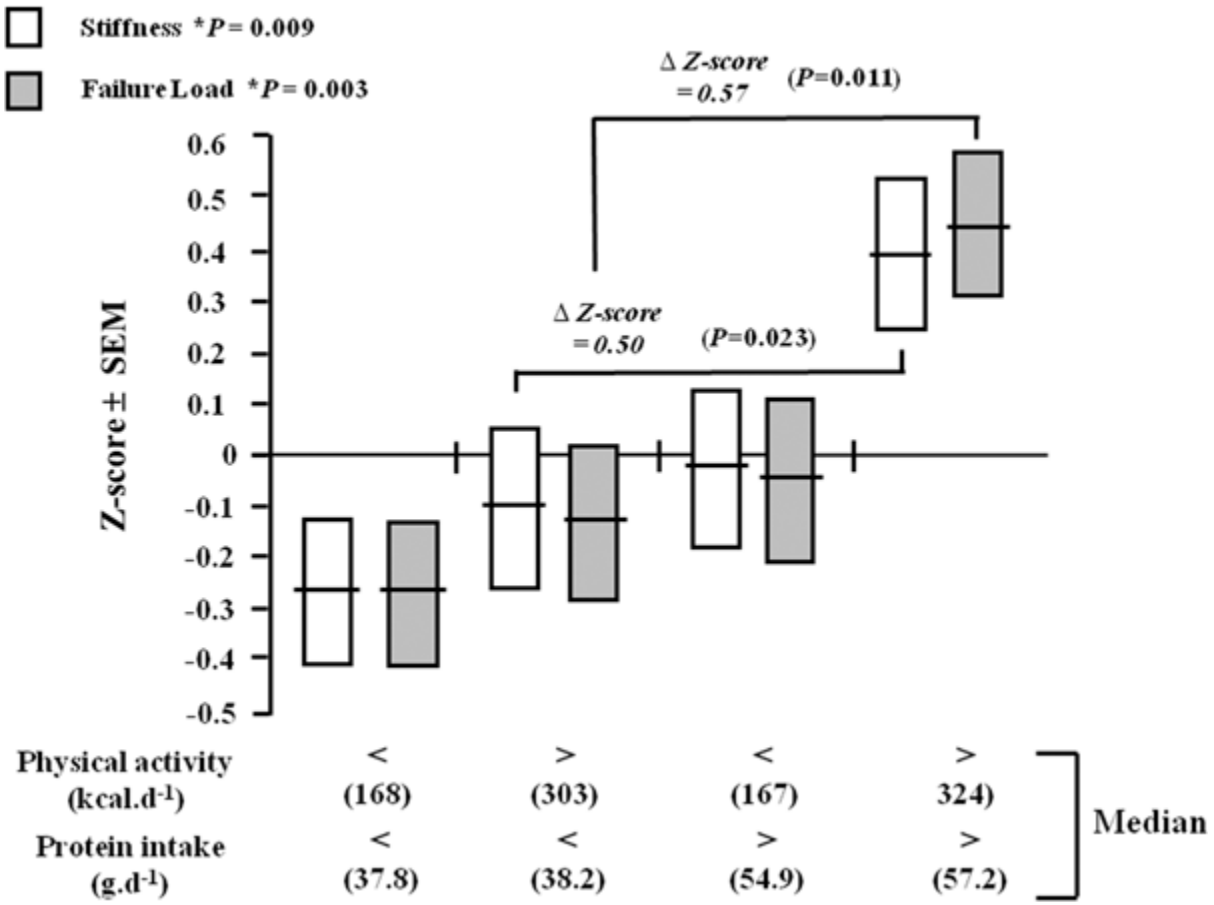
100x, 3 days/wk
for 7 months





Fuchs RK, Bauer JJ, Snow CM. Jumping Improves Hip and Lumbar Spine Bone Mass in Prepubescent Children: A Randomized Controlled Trial. J Bone Miner Res 2001;16: 148–156)

Protein Intake and Exercise



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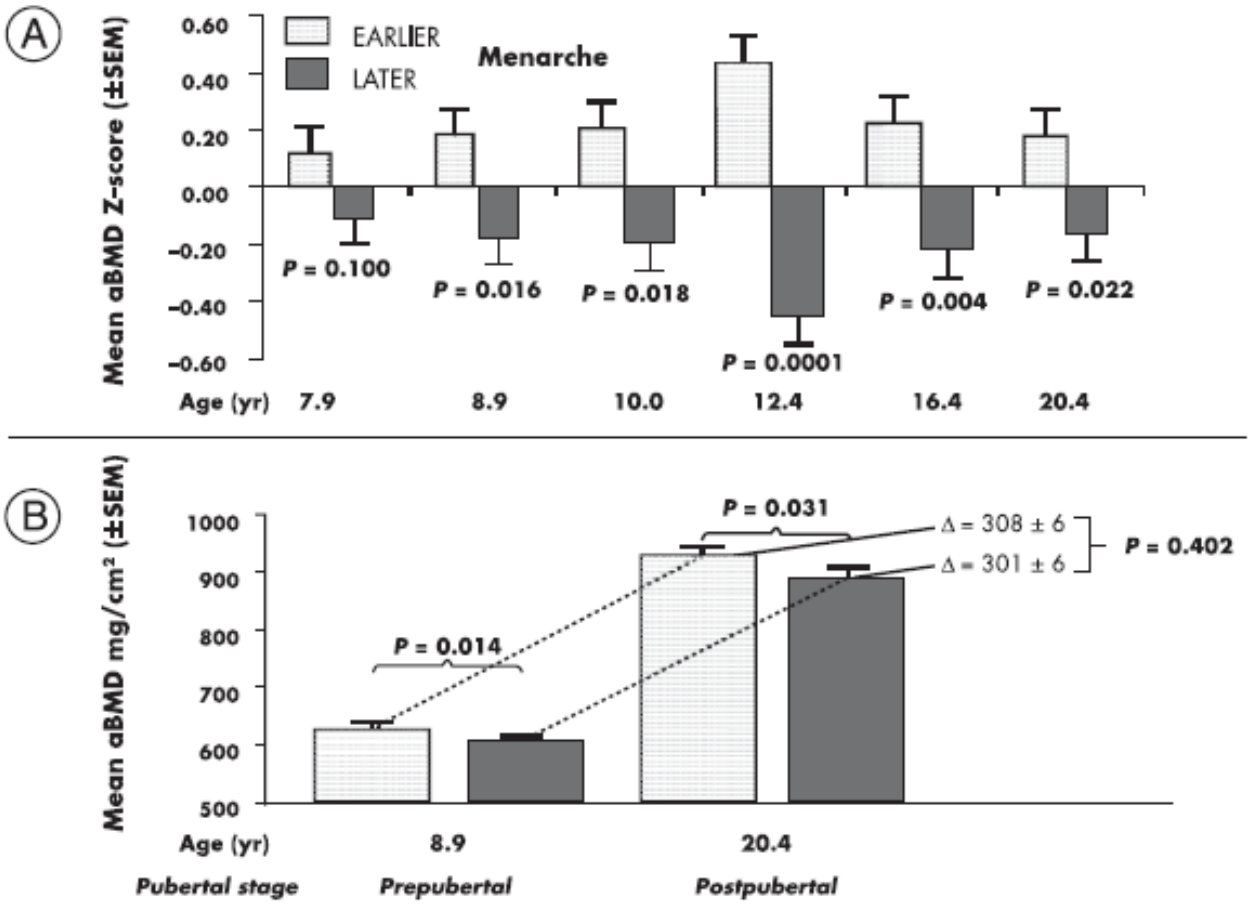
http://onlinelibrary.wiley.com/doi/10.1002/jbmr.2247/full#jbmr2247-fig-0005

Puberty

- 40% of bone mass is accumulated during Tanner 2-5
- Bone density shows a high degree of tracking between childhood and adolescence
  - Healthy children with low bone density will likely continue to have low bone density

Late Puberty



(Bonjour and Chevalley. Endocrine Reviews. 2014)

Estrogens

- Low dose estrogens lower estradiol levels to subphysiologic levels
- Low doses may be detrimental to bone health
  - 20 mcg of EE appear to lose 1.5% BMD per year
- Less deleterious effect than DMPA alone
  - (1/3-1/2 rate of loss compared to DMPA)
- More deleterious effect at younger ages of use
- 7 days of placebo every 28 days allows for greatest recovery time
- Unknown if discontinuation allows complete recovery

(Ziglar and Hunter. J Pharm Pract. 2012 Jun;25(3):331-40. doi: 2012)

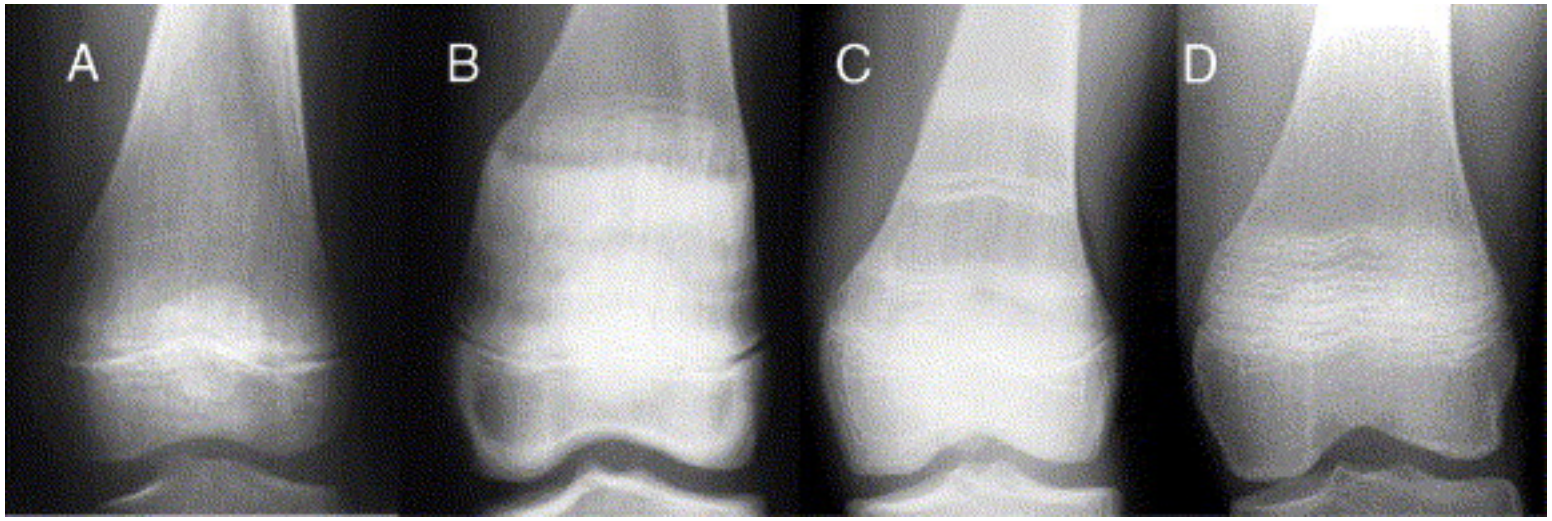
Progestreone (DMPA)

- DMPA use for 2 years
  - Lumbar spine BMD loss of 5.7-6.8%
  - Hip BMD loss of 3.6-5.8%
- In 2004, FDA issued Black Box warning to limit use to 2 years
- Discontinuation of DMPA allows full recovery of BMD
  - Lumbar spine improves to control in 1.1 years
  - Hip improves to control is 4.6 years

(Ziglar and Hunter. J Pharm Pract. 2012 Jun;25(3):331-40. doi: 2012)

Bisphosphonate treatment for osteoporosis in kids

- Used because of some clinical trials in adults suggesting some benefit
- Data in children with osteogenesis imperfecta shows reduction in fractures
- BUT
  - Not FDA-approved indication
  - Remains controversial because of inadequate long-term efficacy and safety data.
  - Limited to extremely severe cases

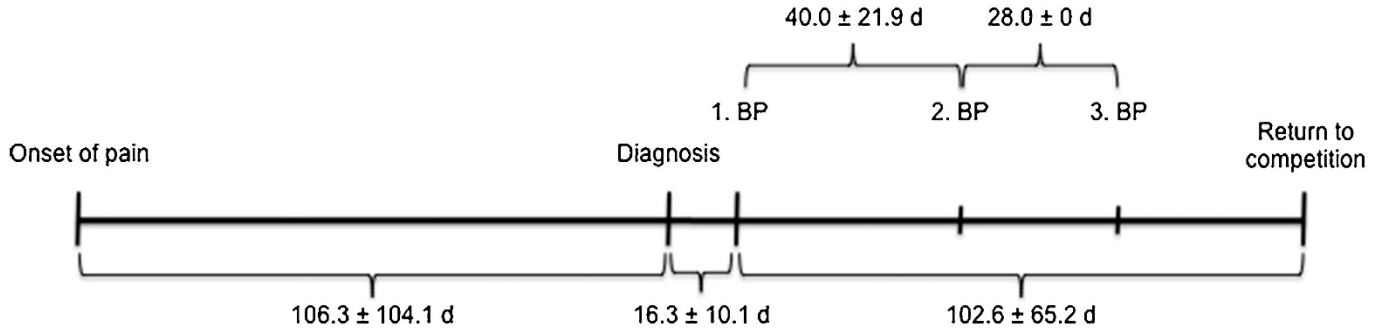


Representative radiographs from specific patient cases treated with various doses of pamidronate. (A and B are same patient before and after treatment).

(Ward K, Cowell CT, Little David G. **Quantification of metaphyseal modeling in children treated with bisphosphonates.** Bone, Volume 36, Issue 6, 2005, 999–1002)

Intravenous bisphosphonates and vitamin D in the treatment of bone marrow edema in professional athletes

- Retrospective chart review
- Included 25 high-performance athletes (88% men), average age 25 ± 4 years
- Diagnosed with bone marrow edema by MRI (4 with stress fractures)
- Complaint of pain significant enough to limit or prevented in their sports
- Treated with ibandronate 3 mg IV monthly as needed for resolution of pain and return to competition



(Injury (2014) 45;6:981-987)

SUMMARY

Optimize diet and physical activity.
Fix any hormonal problems.
Bisphosphonates for the worst cases.

Referrals

WHO?

- Fracture in child with chronic illness/disorder
- Otherwise healthy child with multiple long bone fractures (2 fx < 10 years old, 3 fx > 10 years old)
- Fractures that don't make sense for the degree of trauma
- Recurrent stress fractures in an athlete

WHERE?

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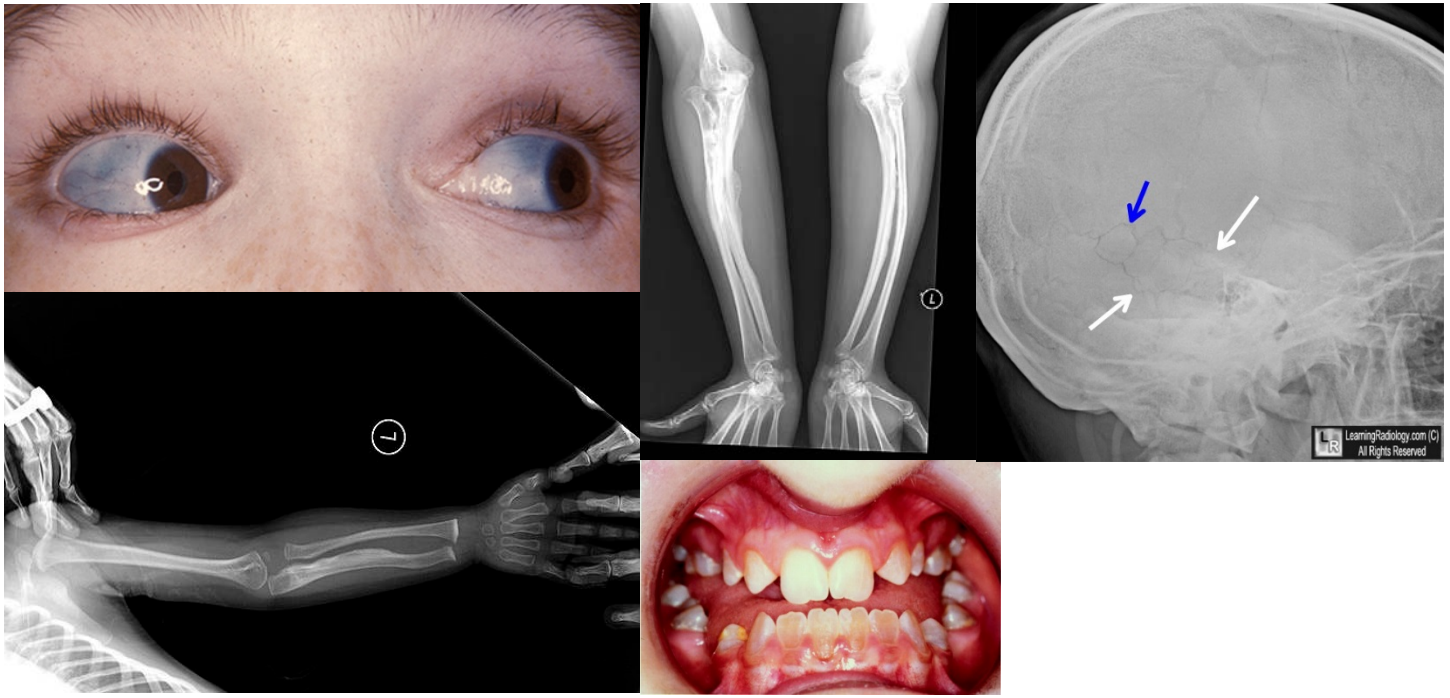
Example of Primary Osteoporosis

- 3-5/12 yo female with two fractures
- 1) At 17 months, standing on hardwood floor, fell landing with one leg on top of the other. X-rays: Right femur fracture
- 2) At 3 yo, standing, mom heard snap, X-rays: non-displaced distal tibial metadiaphysis fracture

Physical Findings



Presentation of OI is highly variable:

- Mild form - no deformity, normal stature, and few fractures
- Severe form – with deformities, hearing and tooth involvement, frequent fractures, scoliosis

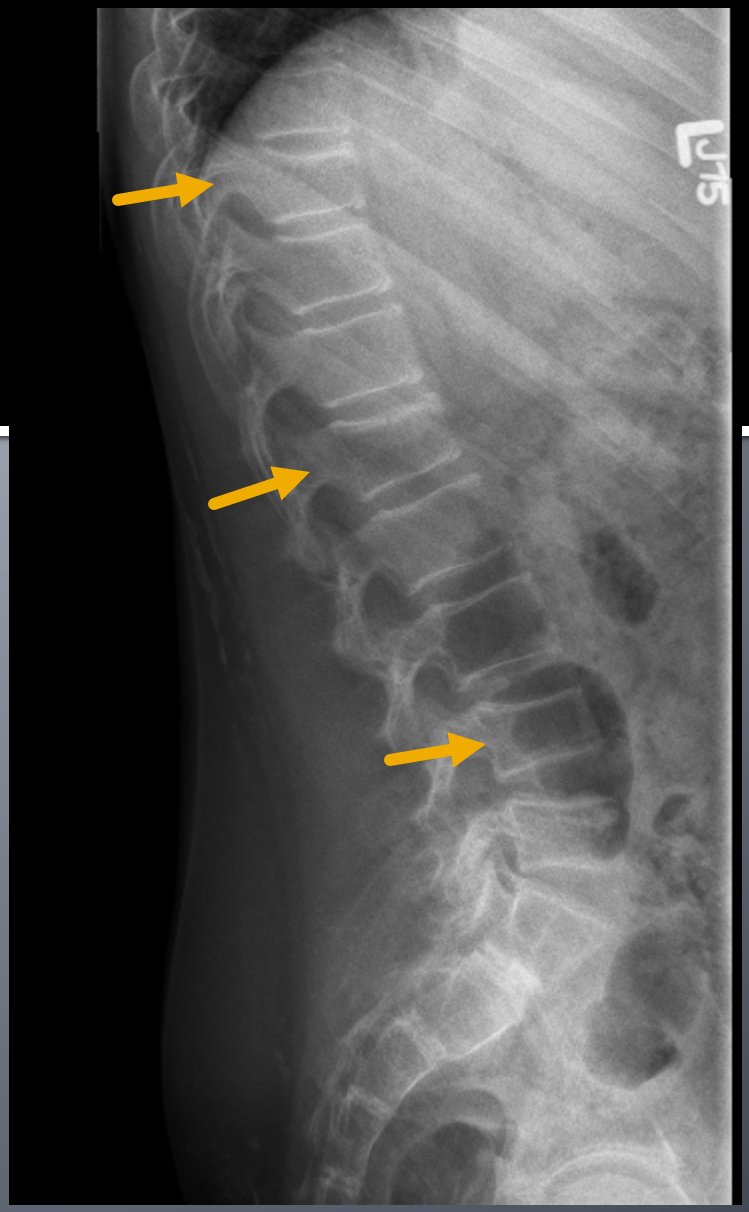
Treatment availability is expanding.

People with OI have lifelong medical issues, but they often lead healthy, productive lives.

Example of Secondary Osteoporosis

- 17 yo male with chief complaint of short stature
- HPI: diagnosed with a diffuse inflammatory connective tissue disorder at 12 years of age, treated with myriad of medications, including prednisone (10-60 mg daily for the past 5 years, 1 year off), wheelchair bound for several years, although now able to ambulate, non-specific back pain
- Exam: Ht 154 cm (60.6 inches); Wt 54.8 kg (120 lbs). Cushingoid features. Tissue calcinosis. Tanner Stage G2PH2.
- Labs: Testosterone consistent with early puberty, otherwise normal labs
- X-rays: Bone age = 15 years; Lumbar spine = 3 vertebral body compression fractures (T10, L1, and L4)
- Diagnosis: Secondary osteoporosis, pubertal delay, short stature
- Tx: Testosterone 100 mg IM monthly, pamidronate 30 mg IV q3 months

Lateral Spine X-Ray



3 vertebral compression fractures

Chronic illnesses –
Optimizing control while minimizing osteotoxic medications

- *Cancer*
- *Celiac disease*
- *Chronic renal disease*
- *Cystic fibrosis*
- *Eating disorders*
- *Endocrine Disorders*
- *Neurofibromatosis*
- *Gaucher's disease*
- *Hemophilia*
- *HIV/AIDS*
- *Muscular dystrophy*
- *Nephrotic syndrome*
- *Malabsorption syndromes*
- *Inflammatory bowel disease*
- *Osteogenesis Imperfecta*
- *Sickle cell disease*
- *Seizure disorders*
- *Systemic lupus erythematous*

Prevalence of Fractures in Children by Disease

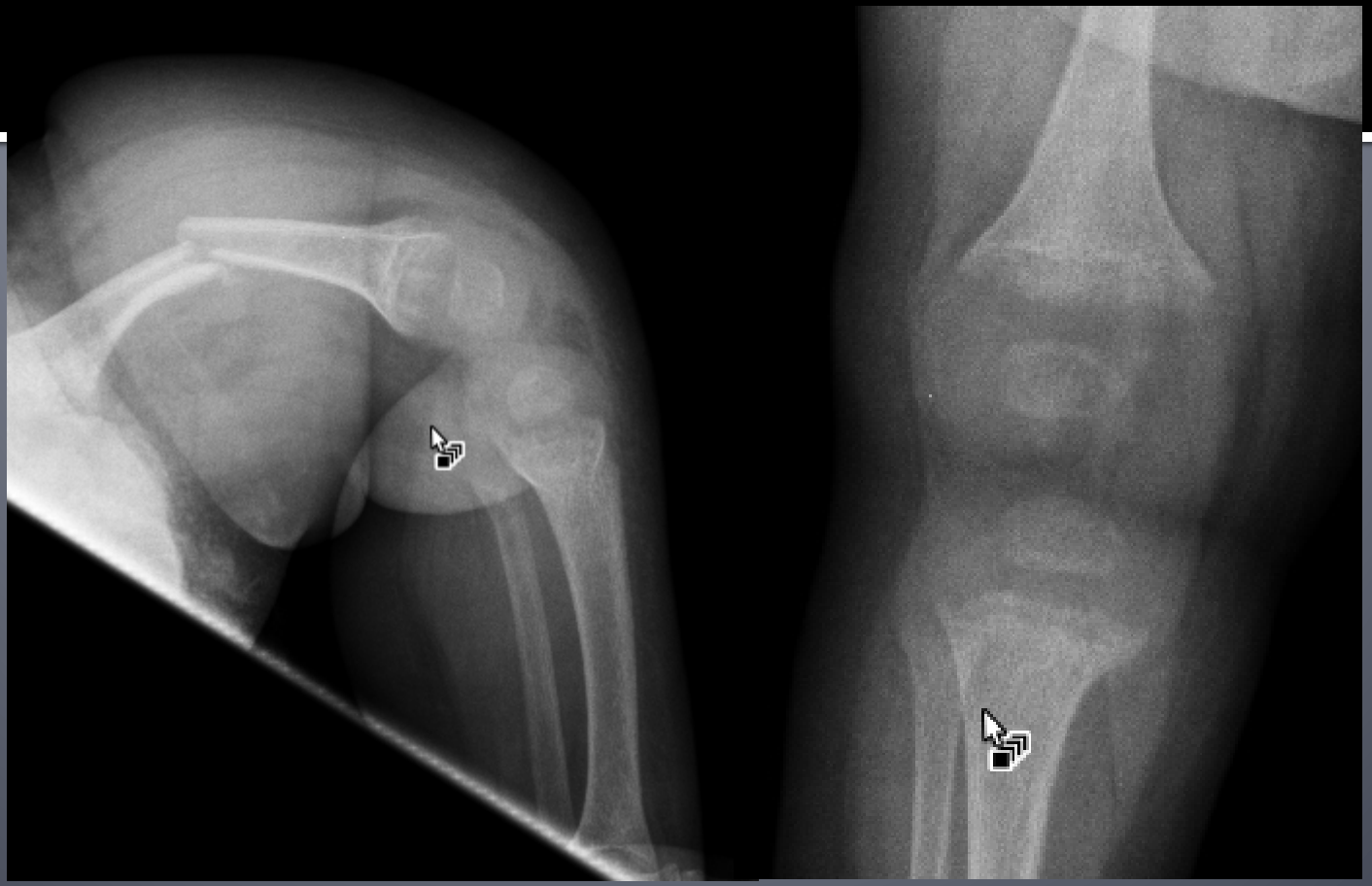
Disease	No. of patients	Fracture location	Prevalence
Cerebral palsy	619		27%
Thalassemia or sickle cell disease	136	limb	17%
	150	verterbrae	13%
Spina bifida	221	limb	20%
Rheumatic disease	90	verterbrae	19%
	117	verterbrae	5% (1 year after GC initiation)
	134	verterbrae	12.4% (3 years after GC initiation)
Leukemia	155	vertebrae	16% (12 months after diagnosis)
	186	vertebrae	26% (4 years after diagnosis)
Duchenne muscular dystrophy	143	vertebrae	32%
Nephrotic syndrome	80	vertebrae	8%
Osteogenesis Imperfecta	58	vertebrae	71%
Recurrent limb fractures	66	vertebrae	29%
Transplants			
Renal	106	vertebrae	8%
	86	vertebrae	20% (15 years post-transplant)
Liver	40	vertebrae	18%
Solid organ	40	vertebrae	35%
	196	vertebrae	18% (average of 9 years after transplant)
	196	limb	27%
	196	all	40%

(Ward LM, Konji VN, Ma J. The management of osteoporosis in children. *Osteoporos Int.* (2016) 27:2147-2179)

Example of metabolic bone disease

- 13 month old male with leg swelling
- HPI: Playing in room with older brother, parents heard a crash. Infant was crying and noted to have leg swelling.
- PMH: healthy, born full term
- FH: no frequent fractures, no bowing of legs
- SH: Infant born in US; parents speak limited English, first language is Bengali

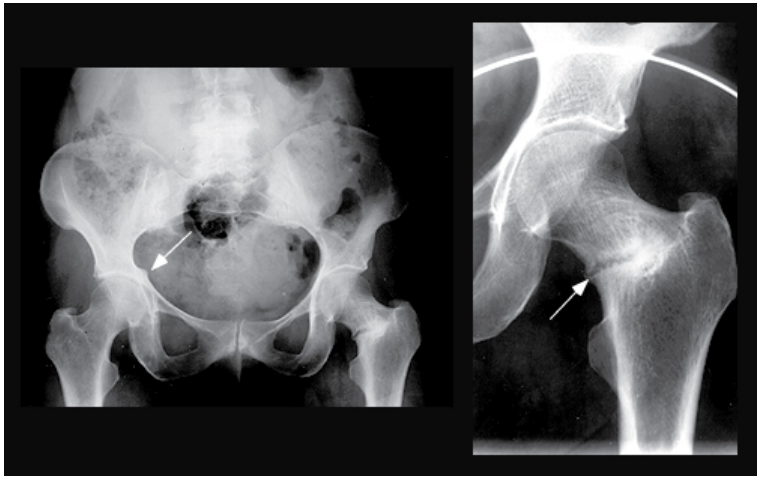
X-Rays



Additional Physical and Radiological Findings





Rickets and Osteomalacia

	PTH	Serum Calcium	Serum Phosphate	Alkaline Phosphatase	25-OH D3	1,25 $(OH)_2$ D3	Urine Calcium	TMP/GFR
Nutritional Deficits								
Vitamin D deficiency	↑	↓ - nl	↓ - nl	↑	↓	↓ - ↑	↓	↓
Calcium deficiency	↑	↓	↓ - nl	↑	nl	nl - ↑	↓	↓
Genetic Disorders								
Hypophosphatemia	↓ - nl	nl	↓	nl - ↑	nl	↓ - nl	nl	↓
Vitamin D resistance	↑	↓ - nl	↓ - nl	↑	nl	↑	↓ - nl	↓ - nl
Hypophosphatasia	nl	nl -↑	nl -↑	↓	nl	nl	nl -↑	↓ - nl

If 25-OH vitamin D is normal, calcium intake is adequate and the child still has rickets, please refer.

Calcium – dietary sources

Common Food Sources of Calcium			
Food	**Serving Size**	**Amount**	**%DV***
Yogurt, fruit, low fat	1 cup	345 mg	35%
Milk, low fat	1 cup	305 mg	31%
Orange juice, calcium fortified	1 cup	300 mg	30%
Sardines, canned with bone	3 ounces	325 mg	33%
Collard greens, boiled	1 cup	266 mg	27%
Cereal, cream of wheat, cooked	1 cup	232 mg	23%
Cheese, cheddar	1 ounce	204 mg	20%
Beans, white, boiled	1 cup	191 mg	19%
Fish, salmon, canned	3 ounces	181 mg	18 %
Soybeans, boiled	1 cup	175 mg	18 %
Cottage cheese, low-fat	1 cup	138 mg	14%
Kale, boiled	1 cup	94 mg	9%
Beans, pinto, boiled	1 cup	79 mg	8%
Almonds	1 ounce	75 mg	8%
Broccoli, boiled	1 cup	62 mg	6%
Figs, dried	2 figs	62 mg	6%
Oranges, raw	1 medium	52 mg	5%

Source: USDA Nutrient Database.

* Daily Value (DV) is the daily reference amount used on food and supplement labels.

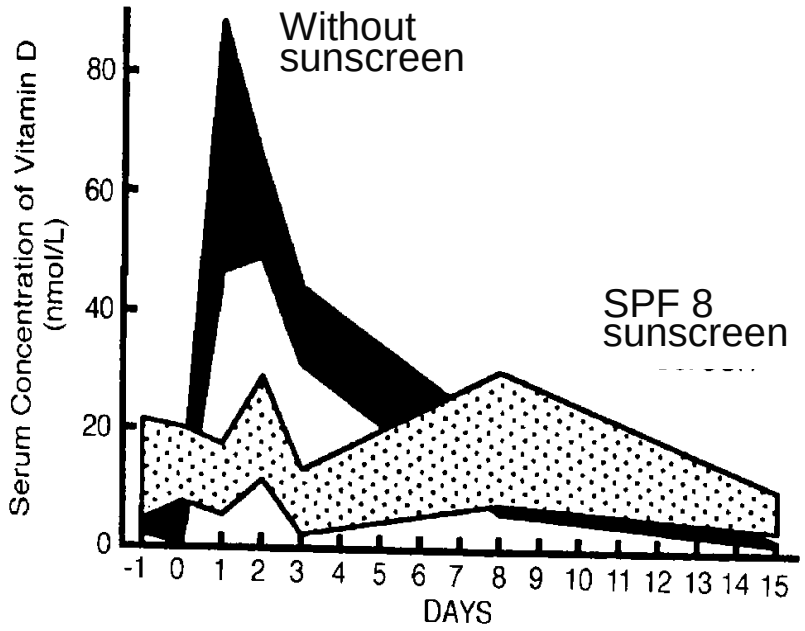
Vitamin D

Vitamin D Sources

- From the sun:
  - Blocked by epidermal melanin
  - Requires direct UVB radiation (which occurs ~10AM-3PM in spring, summer, and fall)
    - In summer, for pale skin: 4-10 min; dark skin 60-80 min assuming 20% of skin exposed
    - In winter, UVB rays above 37 degrees latitude are decreased by 80-100%
- In Food:
  - Less than 10% is derived from dietary sources
- In Breastmilk:
  - Averages 22 IU/L (range 15-50 IU/L)
  - Supplementing mothers with 4000-6400 IU daily may suffice
- In supplements:
  - Cholecalciferol content of OTC pills varies greatly (65-130%)
  - Brands with a seal from USP or NSF International have been 3rd party tested to verify pills contain 90% to 110% of the active ingredient

Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. *Pediatrics* 2008;122;398
AND JAMA Intern Med. 2013;173(7):585-586.

Circulating vitamin D levels after 1 MED of simulated sunlight



MED = minimal erythema dose – i.e how long a person can stay in the sun before getting a minor sunburn

Sunlight and Vitamin D

- 5-15 minutes of sun exposure 2-6 times per week to the face, arms, hands, or back without sunscreen is usually sufficient to provide adequate vitamin D (between 10am-3pm)
  - Depends on time of year (see below)
  - African Americans may need six times the UV exposure compared to whites
- Season, latitude, time of day
  - Above 35 degrees north latitude (Atlanta), little or no vitamin D3 can be produced from November to February

Vitamin D – dietary sources

Food	IUs per serving*	Percent DV**
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

* IUs = International Units.

** DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for vitamin D is currently set at 400 IU for adults and children age 4 and older. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also

Vitamin D Deficiency Treatment

TABLE 7 Treatment of Vitamin D–Deficiency Rickets: Vitamin D and Calcium Supplementation and Monitoring of Therapy

Vitamin D (ergocalciferol)
- Double-dose vitamin D: 20 μg (800 IU)/d × 3–4 mo; or
- Pharmacological doses of vitamin D: 25–125 μg (1000–10 000 IU) per day × 8–12 wk depending on the age of the child, then maintain at 10–25 μg (400–1000 IU) per day; or
- Stoss therapy: ~2.5–15.0 mg or 100 000–600 000 IU of vitamin D orally (over 1–5 d), then maintain at 10–25 μg (400–1000 IU) of vitamin D per day, or 1.25 mg or 50 000 IU of vitamin D_2 weekly for 8 wk orally (teenagers and adults)

Calcium
- 30–75 mg/kg per d of elemental calcium in 3 divided doses (start at a higher dose, and wean down to the lower end of the range over 2–4 wk)

Monitoring of therapy
- At 1 mo: calcium, phosphorus, ALP
- At 3 mo: calcium, phosphorus, magnesium, ALP, PTH, 25(OH)-D, urine calcium/creatinine ratio (frequency depends on severity of rickets and hypocalcemia); recheck radiologic findings in 3 mo
- At 1 y and annually: 25(OH)-D

Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. *Pediatrics* 2008;122;398

Prevention

	Advice
Pregnant and breastfeeding women	
UK Department of Health 2012[100]	All pregnant and breastfeeding women to take a daily supplement containing 10 µg per day of vitamin D
NICE 2008 (CG62)	Supplementation in at risk groups
American Academy Of Pediatrics 2008[97]	Measure maternal vitamin D status and supplement if found to be "insufficient"
WHO 2012*[101]	Call for rigorous randomised controlled trials to evaluate the benefit and safety of routine vitamin D supplementation in pregnancy
Canadian Paediatric Society 2007[102]	50 µg per day for pregnant and lactating women, especially during winter months
Institute of Medicine 2010[53]	Recommended dietary allowance 15 µg per day. Upper level intake 100 µg per day
Breastfed infants	
UK Department of Health 2012[100]	If mother has not taken supplements throughout pregnancy baby might need to receive drops from 1 month of age
Canadian Paediatric Society 2007[102]	5 µg per day (200 IU per day) for premature infants, 10 µg per day (400 IU per day) until 1 year of age, but 20 µg per day (800 IU per day) during winter and for those living at more northern latitudes than the 55th parallel or between 40 and 55th parallel with additional risk factors
Institute of Medicine 2010[53]	10 µg per day (400 IU per day) during first year of life
Children and adolescents	
American Academy Of Pediatrics 2008[97]	Universal supplementation of 10 µg per day (400 IU per day), greater doses for at risk groups
UK Department of Health 2012[100]	7–8·5 µg per day (280 IU per day) in all children aged 6 months until the age of 5 years

*Advice based on conclusions from Cochrane meta-analysis.[103]

Table 5: **Summary of global supplementation advice by advising bodies**

Elder CJ, Bishop NJ. Rickets. Lancet. 2014 Jan 9. pii: S0140-6736(13)61650-5. doi: 10.1016/S0140-6736(13)61650-5

Maintenance Vitamin D recommendations

- Vitamin D supplementation is recommended in all infants.
- Vitamin D supplementation should be started within the first days of life.
- Recommended vitamin D intakes for children and adolescents without risk factors for vitamin D deficiency are:
  - 400 IU/day during the first year of life
  - 600 IU/day after the first year of life (1–18 years)
- Recommended vitamin D intakes for infants, children, and adolescents with risk factors for vitamin D deficiency are:
  - 400–1,000 IU/day during the first year of life
  - 600–1,000 IU/day after the first year of life (1–18 years)
- Recommended vitamin D intake for preterm infants is 400–800 IU/day
- The exact duration of vitamin D supplementation has not been established. Children without risk factors for vitamin D deficiency could be reasonably supplemented until the age of 2 years, when growth velocity is high.
- In older children, vitamin D supplementation should be tailored to sun exposure and risk factors for vitamin D deficiency.
- While continuous supplementation is advisable in children with risk factors for vitamin D deficiency, children without risk factors—but with limited summer sun exposure—may be supplemented in the late fall and winter only (i.e., between November and April in Europe).
- Children who are obese or who are on anticonvulsant medications, glucocorticoids, or antifungals should receive at least two to three times more vitamin D.

Saggese, Vierucci, Boot, Czech-Kowalska, Weber, Camargo, Mallet, Fanos, Shaw, Holick. Eur J Pediatr (2015) 174:565–576.

Maintenance Therapy Vitamin D for the Less Than Compliant Population

- **50,000 IU by mouth every 4-6 weeks**

Holick MF et al. 2008 JCEM 93(3): 677-681

Gordon CM et al 2008 JCEM 93(7):2716-2721

*Vitamin D and Obestiy

- If BMI > 30 kg/m2, body fat sequesters vitamin D making it less bioavailable to the body
- Obese individuals may need at least twice the amount of vitamin D

Vitamin D daily supplementation

Table 1. Supplemental daily vitamin D_3 requirement in IUs for children and adolescents by body weight and skin color to meet IOM's minimum serum 25(OH)D goal of 20 ng/ml in 95% of the individuals in the target group

		Goal: 20 ng/ml[a]		
Weight range		Skin color		
Kilograms	Pounds	Dark	Medium	Light
0–10	0–22	400[b]	400[b]	400[b]
10–20	22–44	400[c]	400[c]	400[c]
20–30	44–66	400[c]	400[c]	400[c]
30–40	66–88	400[c]	400[c]	400[c]
40–50	88–110	600[c]	400[c]	400[c]
50–60	110–132	600	400[c]	400[c]
60–70	132–154	1,000	400[c]	400[c]
70–80	154–176	1,000	600	400[c]
80–90	176–198	1,000	600	400[c]
90–100	198–220	1,000	600	400[c]
100–110	220–243	2,000	600	400[c]
110–120	243–265	2,000	1,000	600
120–130	265–287	2,000	1,000	600

The table subtracts the dietary amount from the recommended amount and rounds to the nearest available supplement size.
IOM, Institute of Medicine; IU, international unit; 25(OH)D, 25-hydroxyvitamin D.
[a]The IOM considers a serum 25(OH)D level of 20 ng/ml sufficient for bone health but says there is not enough data to determine the optimal level for other functions of vitamin D. [b]The IOM recommends 400 IUs/d for children in their first year. This recommendation is particularly important for breastfed babies. See text for a detailed explanation. [c]The calculated amount is less than the recommended amount.

Weizhaar, Rajan. Pediatr Res. 2015 Feb;77(2):370-5. doi: 10.1038/pr.2014.190.