BONE HEALTH FOR PATIENTS WITH EOS

JILL C FLANAGAN, MD

Children's℠ Healthcare of Atlanta

Dedicated to All Better

DISCLOSURES

- CONSULTANT
  - Orthofix
  - Nuvasive → Internal Limb Lengthening Nails

QUESTIONS

- Do children with EOS at baseline have more osteopenia?
- Does the treatment of EOS worsen accrual of bone mineral density, weaken bone, and/or change the shape of the bone or chest wall?
  - Casting, bracing, or surgery
  - Is the treatment worse on the bone than the underlying problem?
- Do children with EOS have higher fracture rates?
- Do we need to modify treatments in children with known bone disease (such as OI)?

LET'S ASK PUBMED……

PubMed ▼ early onset scoliosis and bone density

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1. Dystrophinopathies.
Darras BT, Urion DK, Ghosh PS.
In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.
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2. Hormonal, metabolic and skeletal phenotype of Schaaf-Yang syndrome: a comparison to Prader-Willi syndrome.
McCarthy JM, McCann-Crosby BM, Rech ME, Yin J, Chen CA, Ali MA, Nguyen HN, Miller JL, Schaaf CP.
J Med Genet. 2018 May;55(5):307-315. doi: 10.1136/jmedgenet-2017-105024. Epub 2018 Mar 1.
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3. Osseointegration improves **bone**-implant interface of pedicle screws in the growing spine: a biomechanical and histological study using an in vivo immature porcine model.
Shiba K, Taneichi H, Namikawa T, Inami S, Takeuchi D, Nohara Y.
Eur Spine J. 2017 Nov;26(11):2754-2762. doi: 10.1007/s00586-017-5062-2. Epub 2017 Apr 8.
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4. Range of Motion in Segmental Versus Nonsegmental Ultrahigh Molecular Weight Polyethylene Sublaminar Wire Growth Guidance Type Constructs for **Early-Onset Scoliosis** Correction.
Roth AK, van der Veen AJ, Bogie R, Willems PC, van Rietbergen B, van Rhijn LW, Arts JJ.
Spine (Phila Pa 1976). 2015 Dec;40(23):E1212-8. doi: 10.1097/BRS.0000000000001078.
PMID: 26244403
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5. Decreased **bone** mineral **density** in patients with neurofibromatosis 1.
Lammert M, Kappler M, Mautner VF, Lammert K, Störkel S, Friedman JM, Atkins D.
Osteoporos Int. 2005 Sep;16(9):1161-6. Epub 2005 Jun 30.

So, now what am I going to talk about???

PubMed ▼ early onset scoliosis and bone mineral

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1. Hormonal, metabolic and skeletal phenotype of Schaaf-Yang syndrome: a comparison to Prader-Willi syndrome.
McCarthy JM, McCann-Crosby BM, Rech ME, Yin J, Chen CA, Ali MA, Nguyen HN, Miller JL, Schaaf CP.
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Osteoporos Int. 2005 Sep;16(9):1161-6. Epub 2005 Jun 30.
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TALK OBJECTIVES

- Discuss normal bone growth/development, especially in early childhood
- Define bone **strength** and the contributions to bone strength
- Understand how EOS treatment may compromise bone strength
- Discuss the role of osteopenia in AIS as well as bracing on relation to bone mineral density in AIS
- Learn alternative surgery and bracing techniques for EOS in known “bad bone” patients

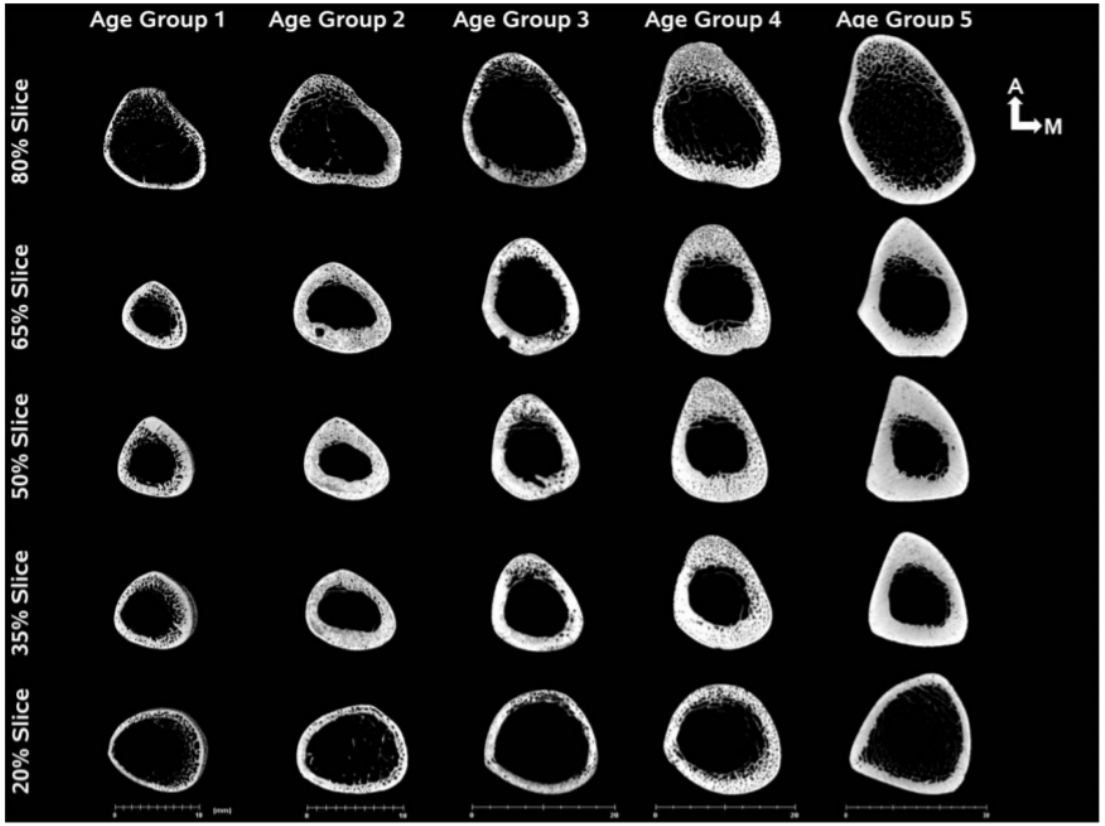
BONE GROWTH

- As bones grow, they undergo a process of modeling and remodeling
- Bone **modeling** involves *uncoupling* of remodeling so that bone shape can be altered to maximize strength
- Bone **remodeling** involves coupling of osteoblasts and osteoclasts with bone formation and resorption respectively

The purpose of modeling and remodeling in childhood is to *obtain* peak bone strength

The purpose of modeling and remodeling in adulthood is to *maintain* bone strength

BONE MODELING OF THE TIBIA

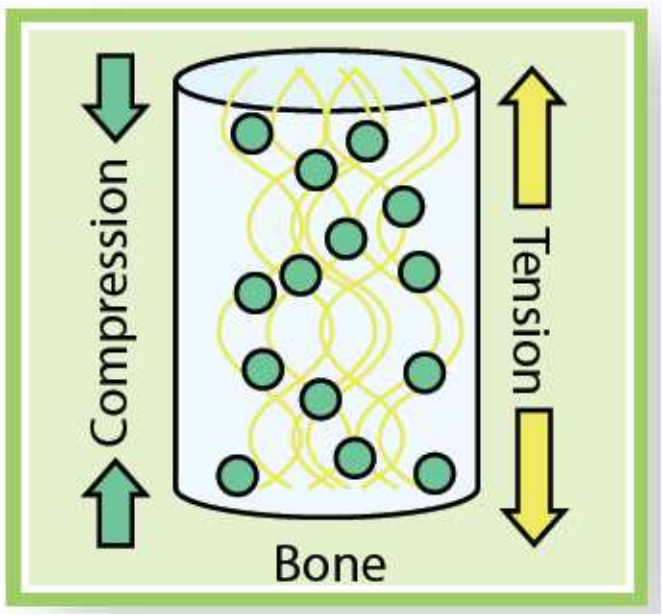


Development of Cortical Bone Geometry, *The Anatomical Record*, 2013

Tibia changes shape from circle to oval due to the mechanical strain on the bone in the AP direction.

STRUCTURE OF BONE – AXIAL VS APPENDICULAR SKELETON

- The structure of bone determines the load it can bear; conversely, the load a bone withstands will contribute to its structure
- **Long Bones**
  - Primarily cortical bone
  - Collagen densely packed
  - Better at withstanding tensile forces
- **Vertebral Bodies**
  - Primarily trabecular bone
  - Bones are more mineralized
  - Better at withstanding compressive forces



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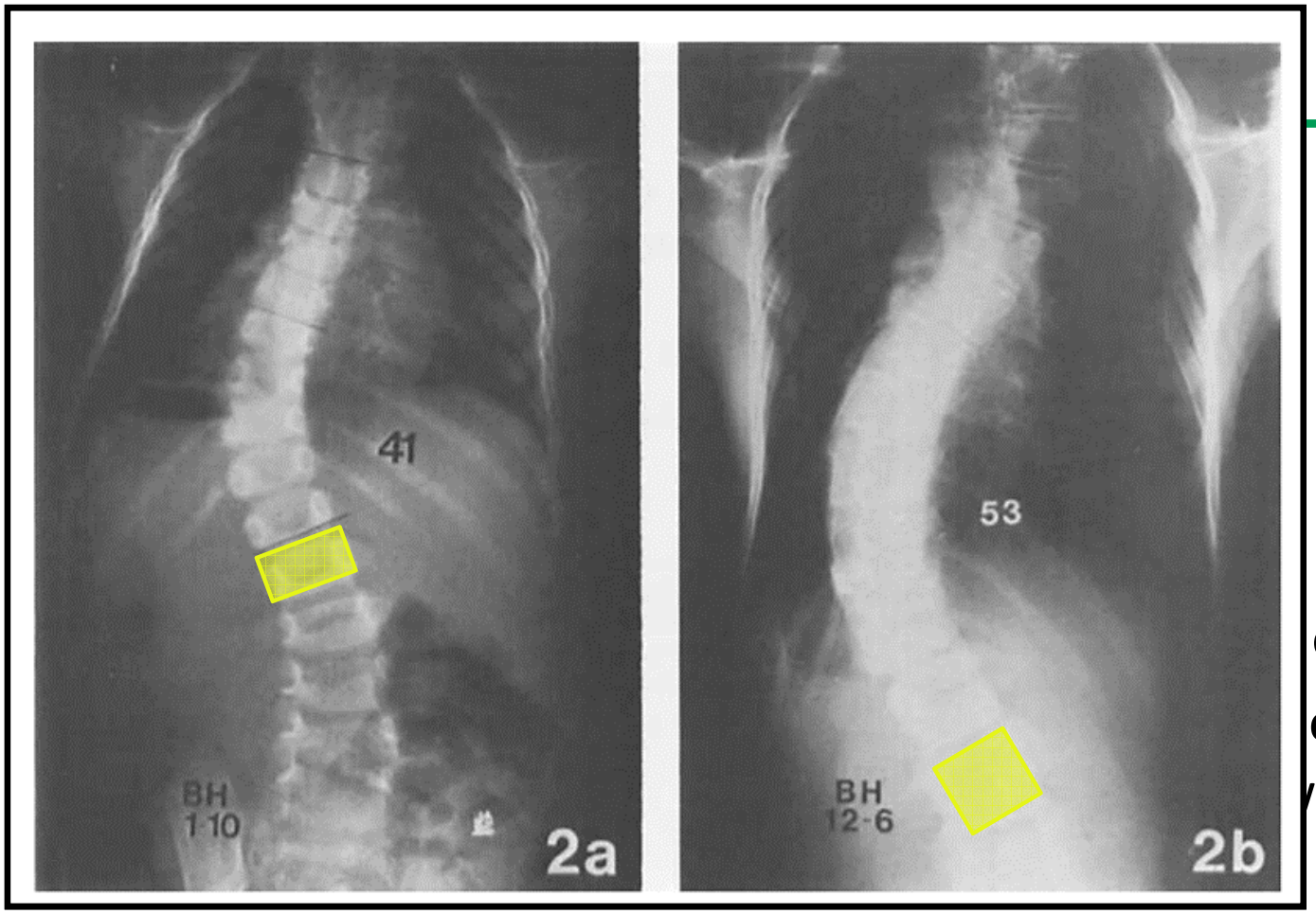


Table 2. Height to width ratio of L2

Age	Controls	B.H.	P.R.	M.H.
1½	1.76	*1.85		
3	1.76	1.57		*1.82
5	1.73	1.55	*1.88	1.58
7	1.63	1.31	1.79	1.44
9	1.65	1.26	1.44	
11	1.80	1.22		1.48
12	1.72		1.34	1.38
13	1.70	1.20	1.21	
15	1.70		1.20	1.36

* indicates the measurement at commencement of cast treatment.

Acta Orthopaedica Scandinavica

Alterations in Vertebral Growth Following Prolonged Plaster Immobilisation

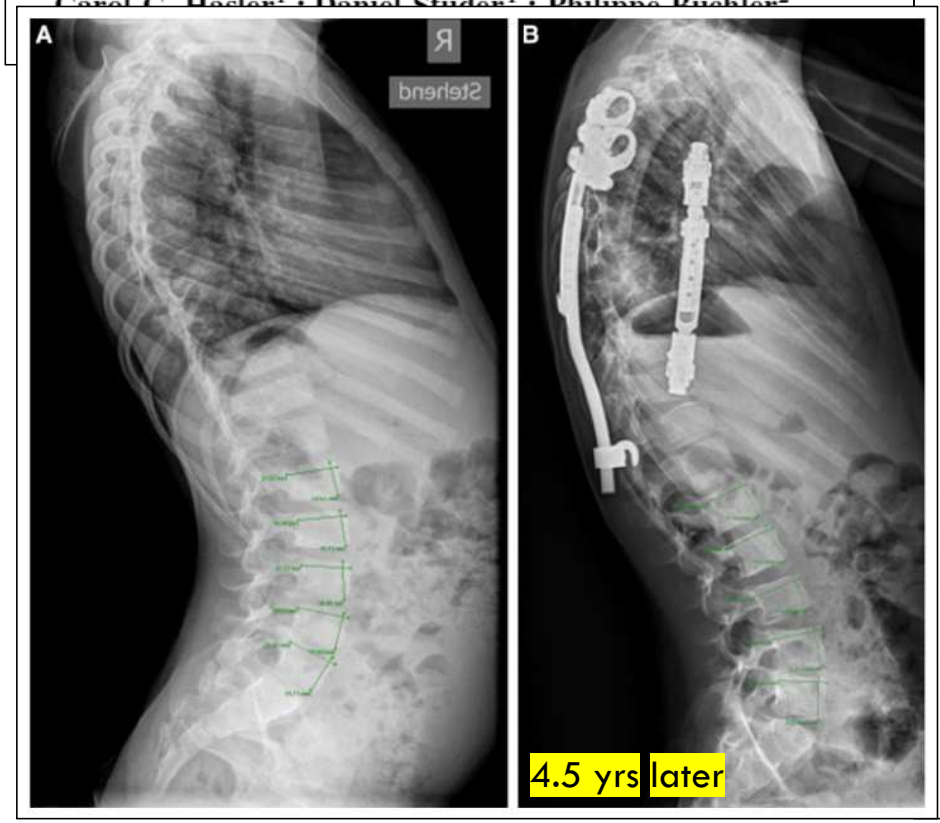
I. W. McCall, E. Galvin, J. P. O'brien & W. M. Park

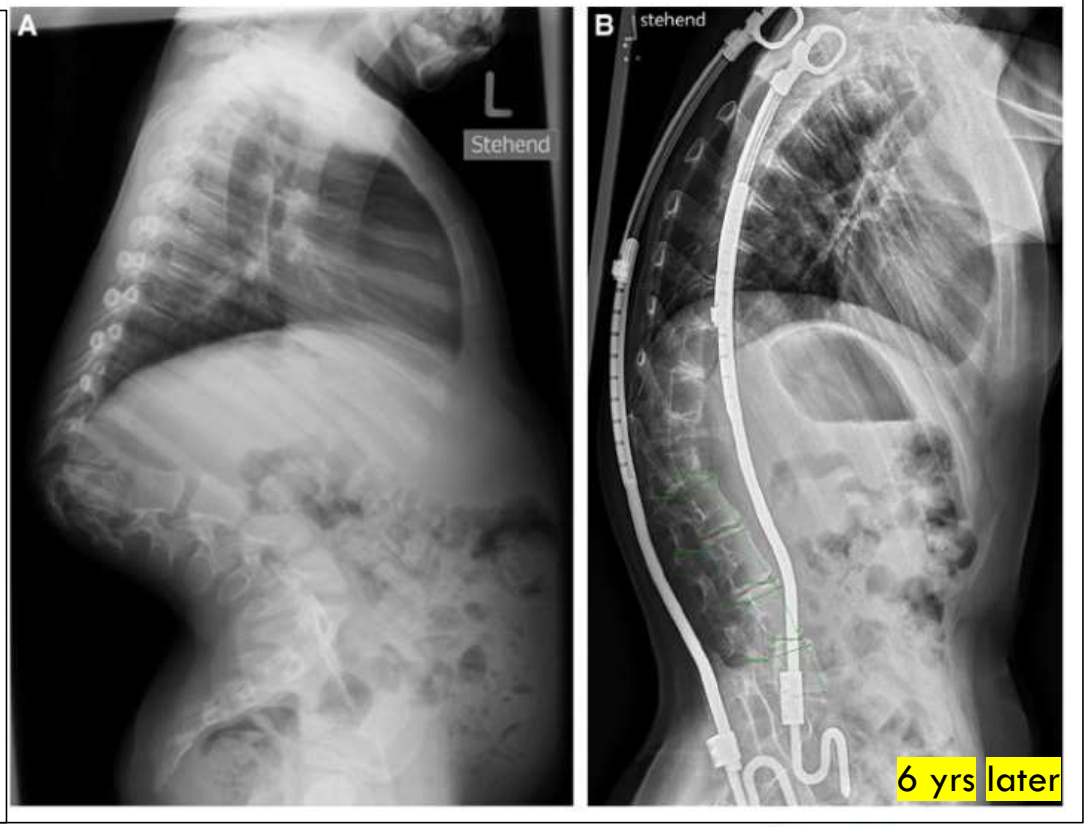
To cite this article: I. W. McCall, E. Galvin, J. P. O'brien & W. M. Park (1981) Alterations in Vertebral Growth Following Prolonged Plaster Immobilisation, Acta Orthopaedica Scandinavica, 52:3, 327-330, DOI: 10.3109/17453678109050110

- "It is therefore probable that the reduction in mechanical force on the growing spine at such an early age is a major factor in this elongation process, especially as it occurs progressively and from the start of treatment and is not related directly to the growth spurt."

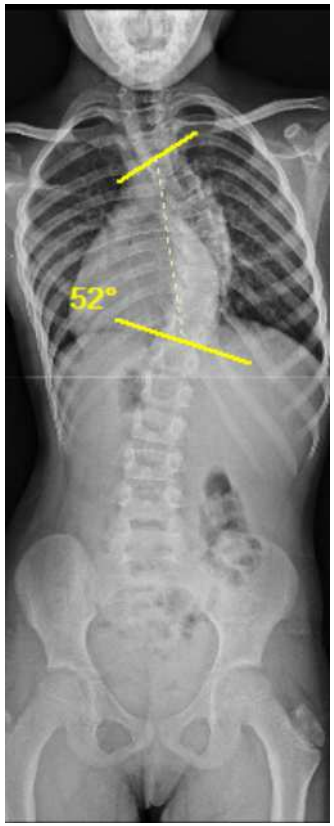
Metamorphosis of human lumbar vertebrae induced by VEPTR growth modulation and stress shielding

Carol C. Hasler[1] · Daniel Studer[1] · Philippe Büchler[2]





Case 1



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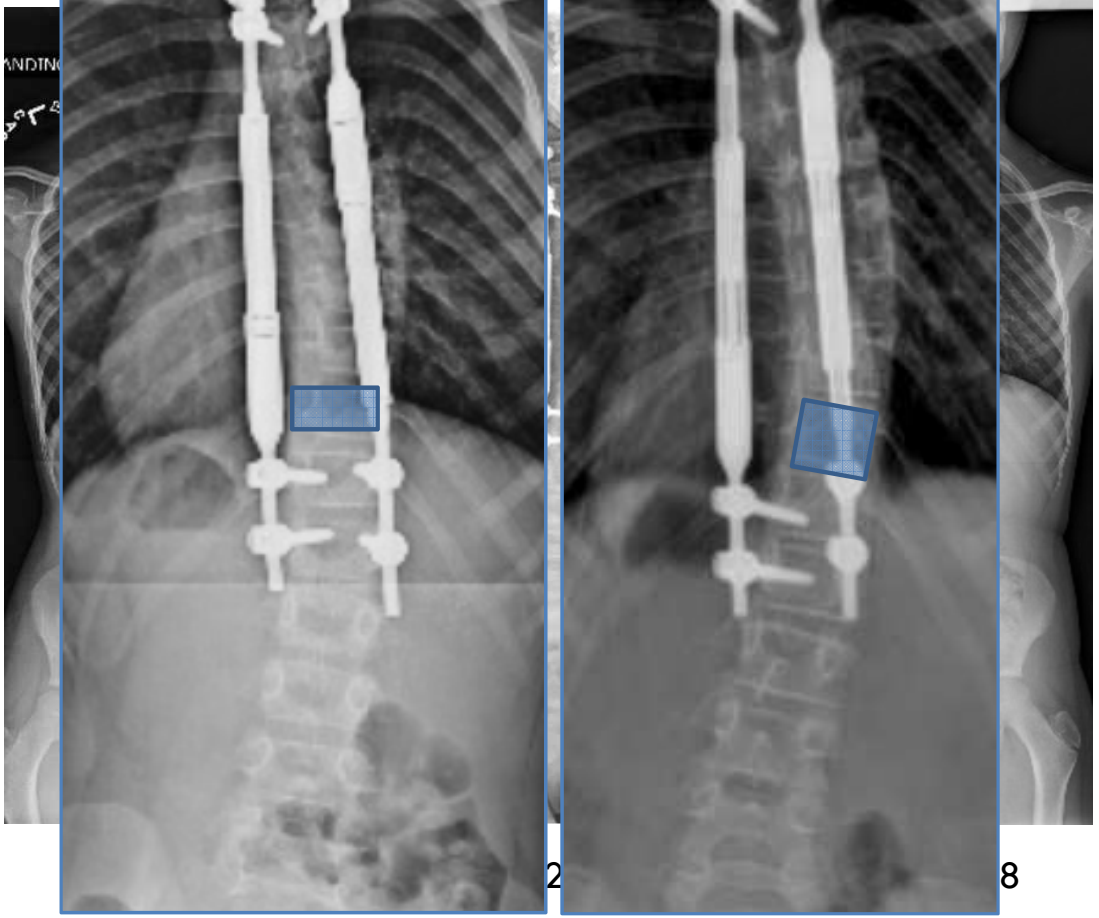

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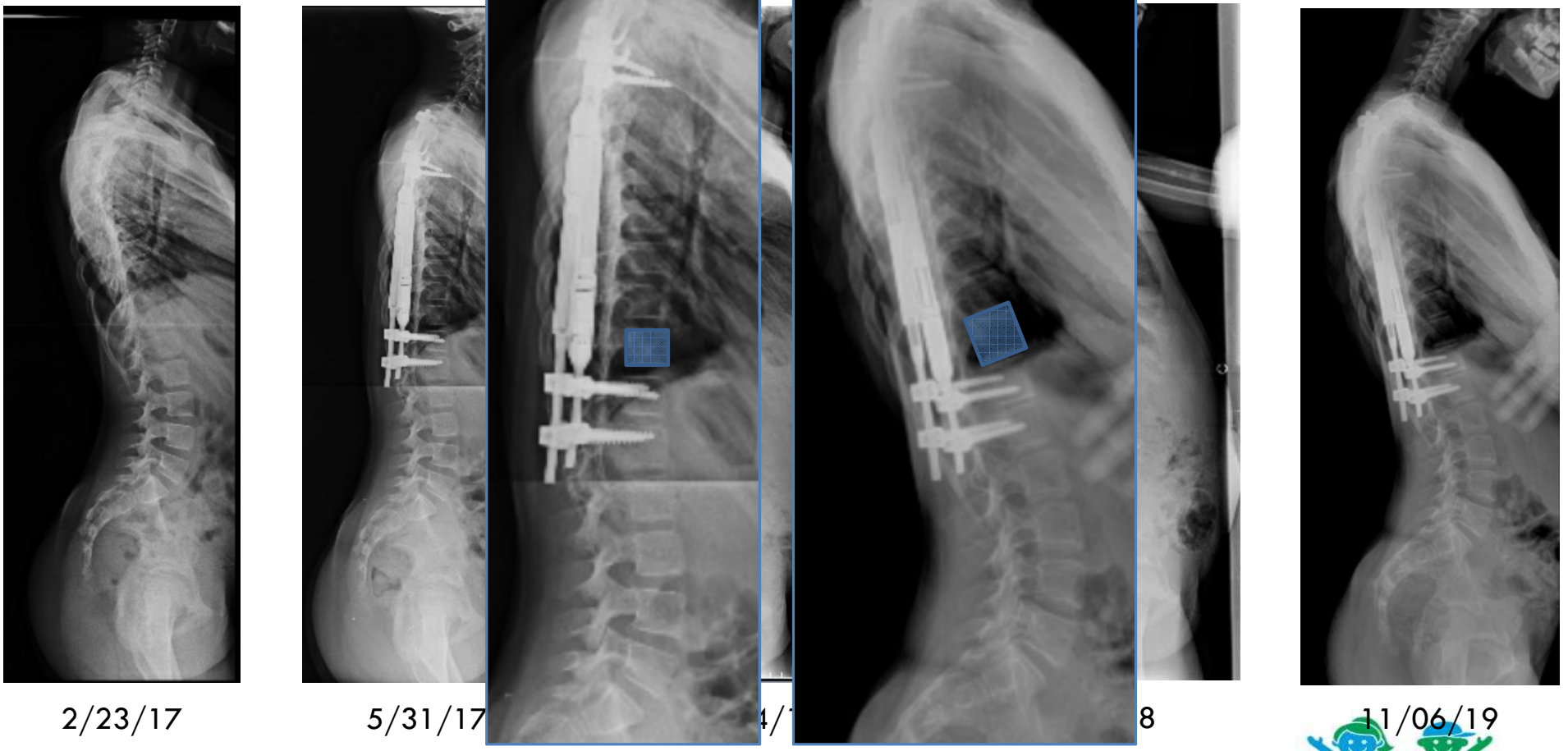

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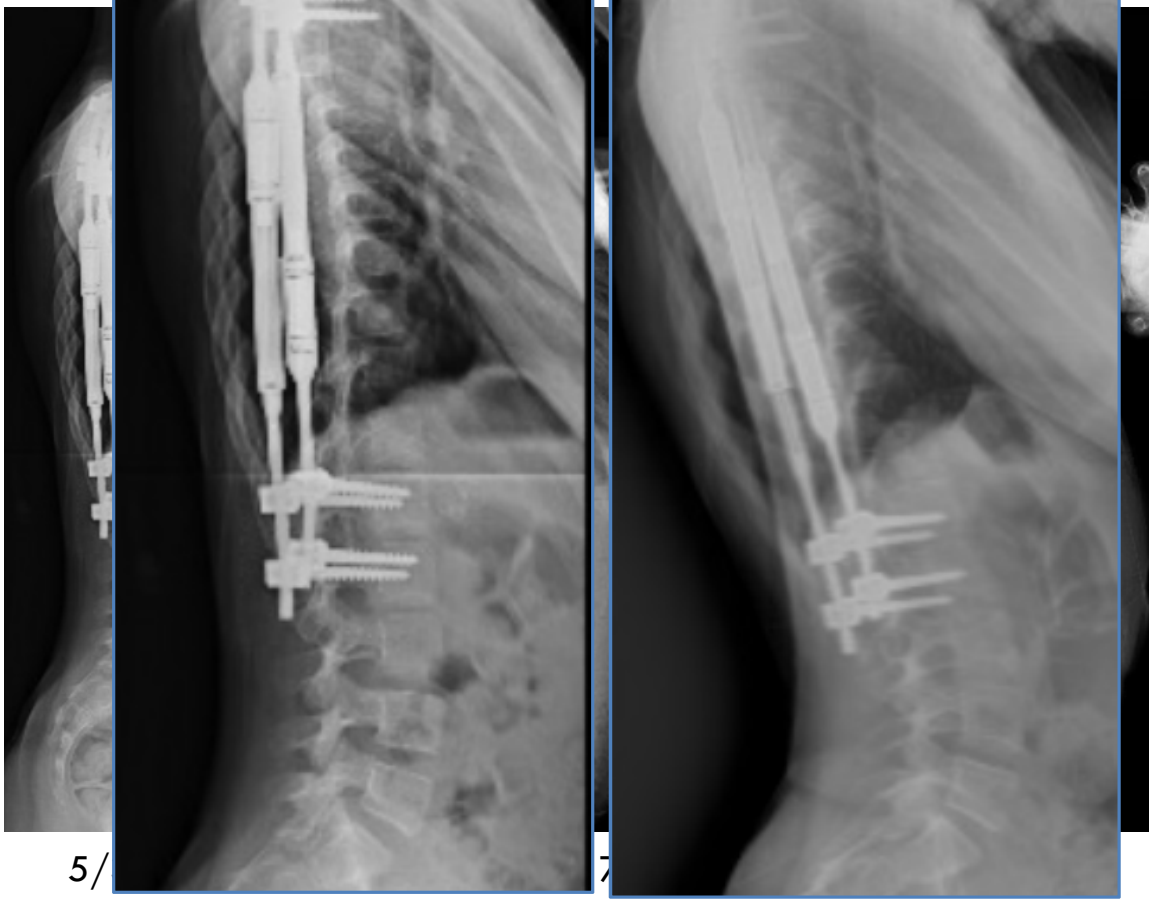
Case 2

2/23/17

11/06/19

Case 2

2/23/17



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11/06/19

WHAT MAKES BONES STRONG ??

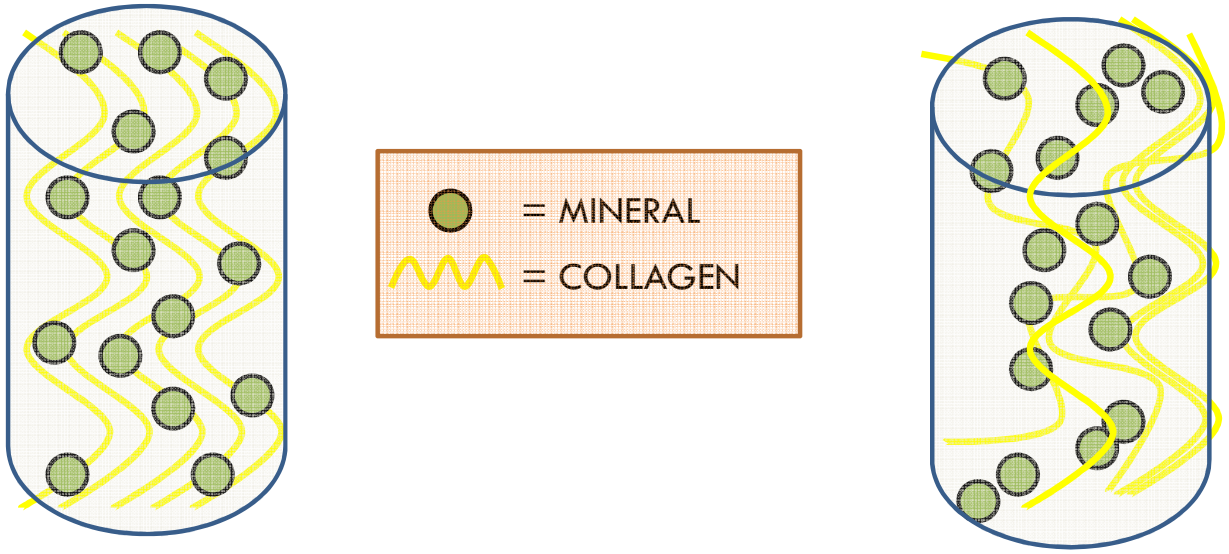
Bone Strength = Material Composition + Structural Design

WHAT MAKES BONES STRONG ?

- COMPOSITION
  - Bone mineral content
  - Rate of bone turnover
  - Healthy osteocytes
  - Integrity of collagen
- DESIGN
  - Bone mineral density
  - Bone shape
  - Cortical thickness
  - Trabecular shape and orientation

While both are important, DESIGN is a more important determinant of bone strength

CONTRIBUTION OF BONE STRUCTURE TO BONE STRENGTH



BOTH BONE MODELS HAVE THE SAME AMOUNT OF COLLAGEN AND MINERAL

HOW TO MAXIMIZE PEAK BONE MASS

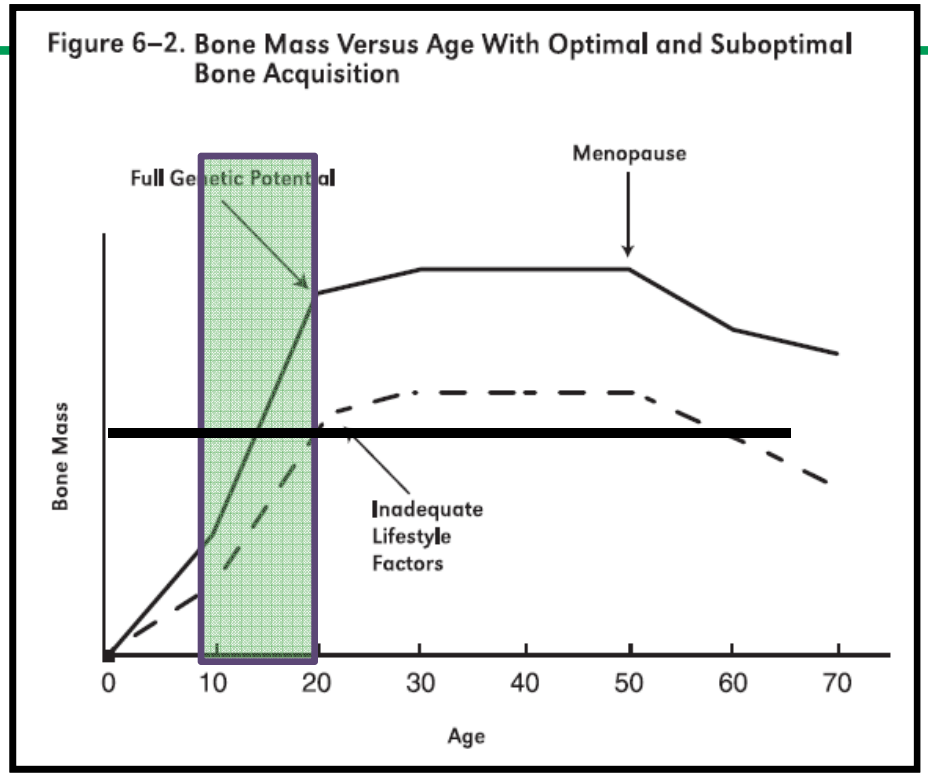
Factors we CANNOT control

- Gender
- Ethnicity
- Hereditary Factors
- Certain Diseases
- *Medications*

Factors we CAN control

- Diet
- Exercise
- Smoking
- Eating Behaviors
- *Medications*

HOW DO WE ACQUIRE BONE MINERAL?



- 60-80% of PBM is genetically determined
- Remainder controlled by "lifestyle factors"

2004 Surgeon General's Report

CALCIUM - HOW MUCH IS ENOUGH??

Based on Institute of Medicine's recommendations, Nov 2010

DAILY REQUIREMENTS OF ELEMENTAL CALCIUM
Infants: 500 mg
Children 1-3 yrs: 700 mg
Children 4-8 yrs: 1000 mg
Children 9-18 yrs: 1300 mg
Adult men/women: 1000 mg

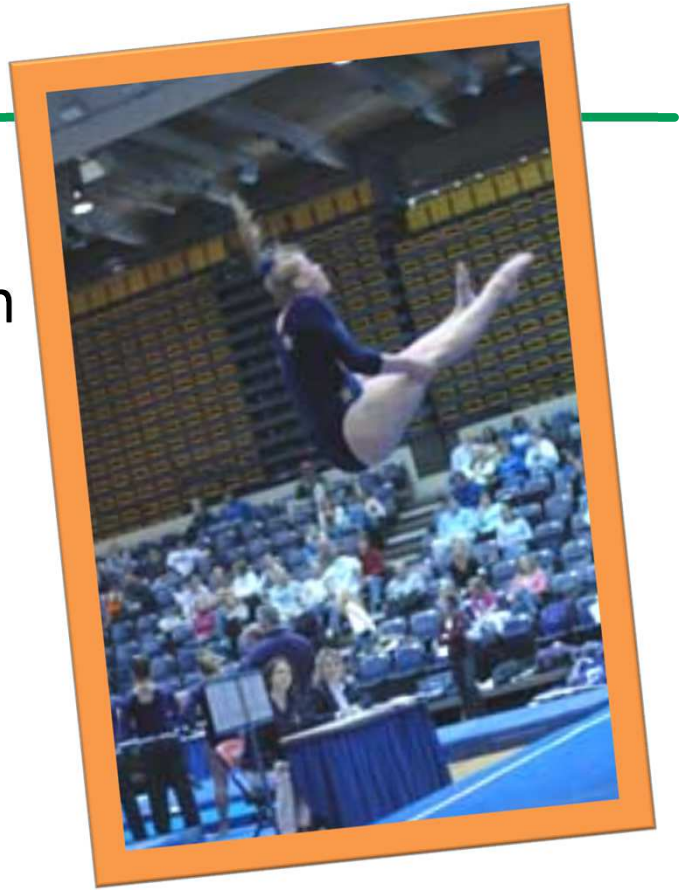
VITAMIN D - HOW MUCH IS ENOUGH?

- Daily requirements of Vitamin D [1]
  - Age 0-1 yr: 400 IU
  - Ages 1-18 yrs: 600 IU
- Breastfed babies should begin supplementation w/in first few days of life [2]
- Formula-fed babies do not need supplementation if drinking 30 oz/d

1. Based on IOM recommendations, Nov 2010
2. AAP guidelines 2008

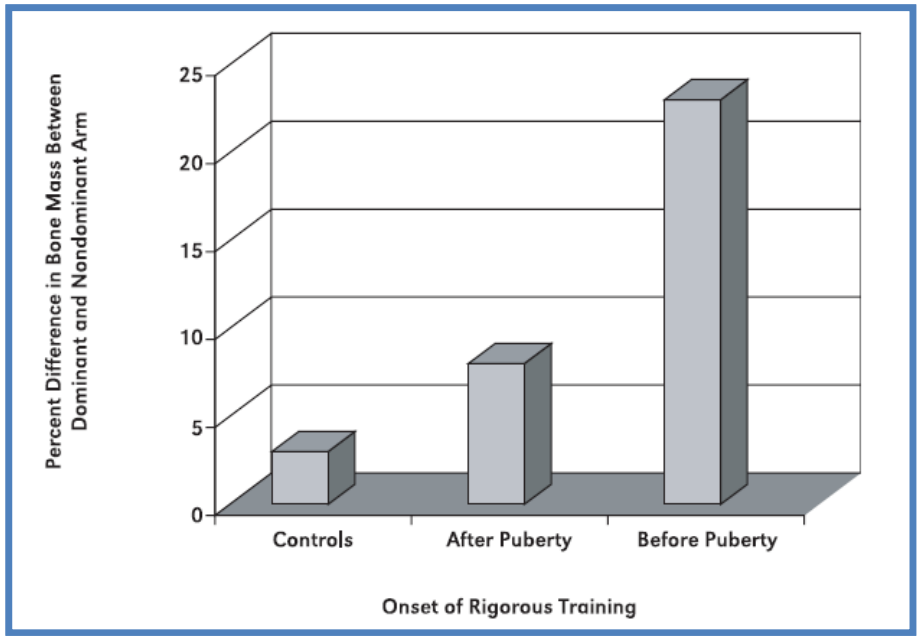
PHYSICAL ACTIVITY

- Physical activity increases the positive impact of calcium on bone mineralization
- During puberty, bone is especially responsive to activity-induced loading
- High intensity jumping improves hip and lumbar spine BMD



PHYSICAL ACTIVITY AND BONE HEALTH

Study that compared BMC of women squash and tennis players of their playing arm with their non-dominant arm



Kannus et al, *Annals of Internal Medicine*, 1995

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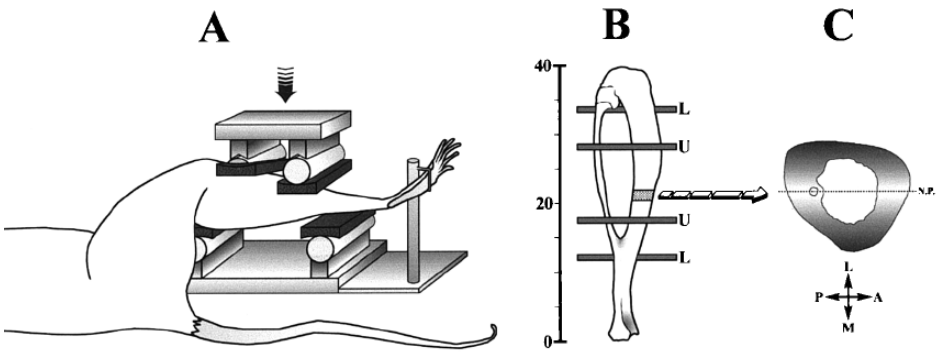
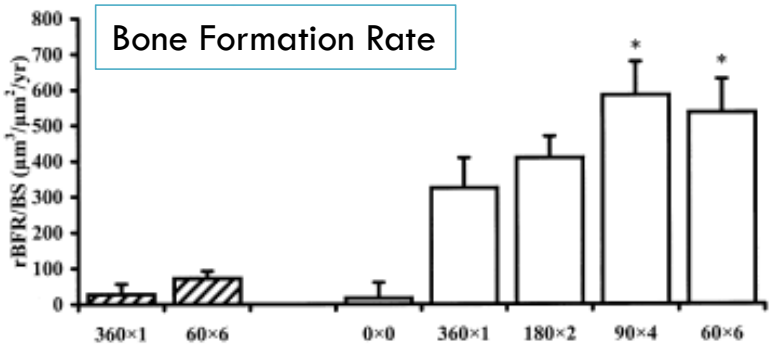
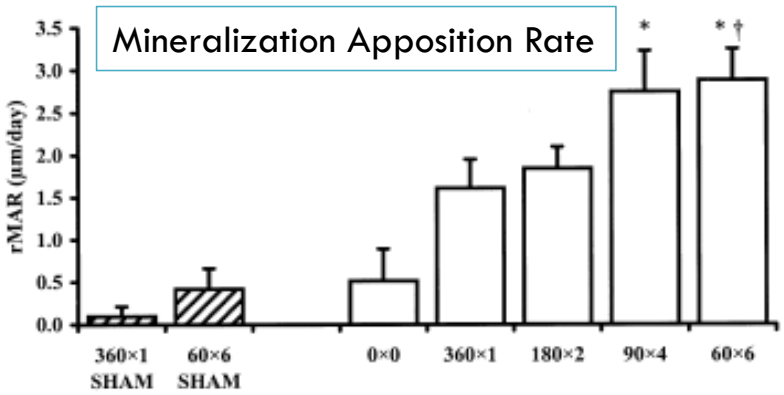
EFFECT OF MECHANICAL LOADING ON BONE

- *JBMR* 2000
- Loaded rat tibias either 360 cycles one per day vs. multiple per day for 3 loading days
- If cycles divided, esp. QID, increase in bone formation rate, and mineralization rate







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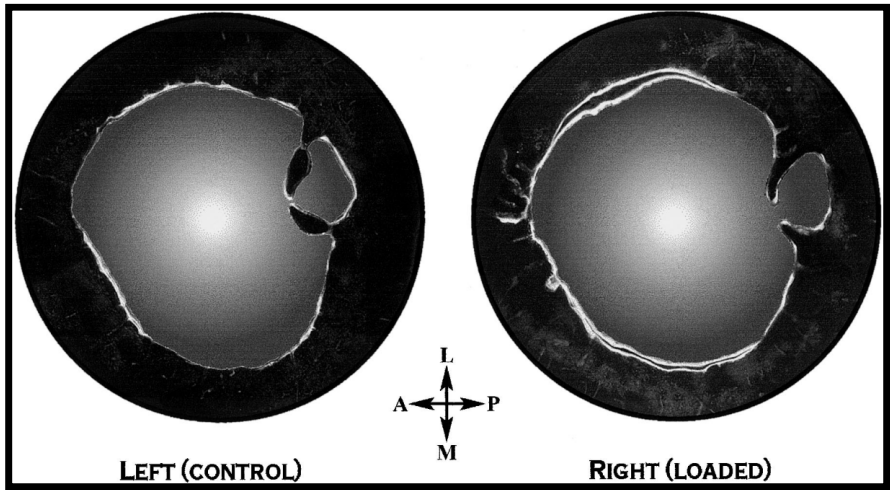
EFFECT OF MECHANICAL LOADING ON BONE



Rat tibia – control vs QID loading, note the endosteal increase in bone, esp M/L at sites of higher strain

- The type of loading can affect bone formation
- The timing of loading can affect bone formation (intermittent more than cyclical)

BONE HEALTH IN AIS

- In 1982, Burner et al[1] first described a relationship between osteopenia and AIS using the Singh index
- Since then, numerous additional studies have supported a relationship between osteopenia and AIS
  - 27-38% of those with AIS found to be osteopenic, and osteopenia found at multiple sites[2]
  - Osteopenia appears to persist into adulthood
- Thought to be due to the disease more so than the mechanical forces involved with scoliosis

1. Burner et al (1982) Osteoporosis and acquired back deformities. *J Pediatr Orthop* 2:383-385.
2. Cheng et al (2005) Osteopenia: A New Prognostic Factor of Curve Progression in AIS. *JBJS* 87A(12):2709-2716

BONE HEALTH IN AIS

- Osteopenia is a significant prognostic factor for curve progression
- Bone mineral densities were found to be similar in bilateral proximal femurs in numerous studies (despite theoretic increased loading based on the convexity of the scoliosis)
- Bracing in AIS was NOT found to affect acquisition of bone mineral during peak height velocity
- In a population of young women treated with bracing for AIS, those found to have osteopenia wore their brace for a much longer duration and had more severe curves than those without osteopenia*

* Cortois et al. (1999) Bone Mineral Density at the femur and lumbar spine in a population of young women treated for scoliosis in adolescence. *Rev Rhum Engl Ed* 66:705-10.

EFFECTS OF BRACING ON BMD IN AIS

Table 4 The association of brace treatment with BMD in AIS

Authors	Conclusion
Cook et al. (1987) [11]	Although the BMD values of the 11 patients treated with bracing were lower than the 30 subjects not treated with bracing, these differences were not statistically significant
Thomas et al. (1992) [41]	The type of treatment including bracing, electrical stimulation and surgery had no effect with respect to the lower lumbar and femoral neck bone mineral densities
Synder et al. (1995) [38]	After adjusting for the magnitude and type of the curve, body mass index (BMI), activity, and diet, they demonstrated that no significant difference of the BMD values of the spine and hip between the brace treatment and observation group in AIS patients
Synder et al. (2005) [37]	Over 1 year period of brace treatment of scoliosis during adolescence did not adversely affect bone density accumulation at the spine or hip. The bone density accumulation was not significantly correlated with reported daily duration of brace use, annual change in BMI, severity of scoliosis
Sun et al.(2006) [40]	Both BMC and BMD levels increased during brace treatment in AIS at a rate similar to reported normal values, and bracing dose not appear to adversely affect the accumulation of bone mass in AIS

Li et al. Low Bone Mineral Status in AIS. *Eur Spine J.* (2008) 17:1431-1440

SO-WHAT DOES THIS MEAN FOR EOS PATIENTS?

- There may be a subset of EOS patients that have osteopenia at baseline
- **Bracing/casting**:
  - Likely does not influence BMD *accrual*
  - Decrease in muscle strain on the spine *may* alter bone modeling and *may* decrease bone strength for at least a transient period of time
  - Osteopenia may increase risks of progression
- **Surgery:**
  - Growth constructs - VEPTR that span the pelvis likely alter the height:depth ratio
  - MCGR may demonstrate similar effects
  - Unclear the long-term effects of stress shielding of spine to these implants
- **Treatments**:
  - Encourage children to jump/exercise to load lower extremities
  - Promote healthy eating habits, ensure appropriate levels of calcium/Vit D
  - Likely a role for bisphosphonate infusion, especially for syndromic EOS

BONE HEALTH WORKUP IN EOS

- **WHO TO WORK UP:**
  - Patients with known bone disorders (such as OI)
  - Patients that are nonambulatory
  - Patients with muscular dysorders (SMA, DMD)
- **HOW TO WORK UP:**
  - Blood Work: CBC, CMP, Calcium, PTH, 25-Vit D, +/- urine calcium
  - Bone Density Testing →
    - make sure you know how low your center's database will go for z-scores
    - Make sure your radiologist knows how to correct for "height age" If needed
- **WHEN TO REFER:**
  - Most likely the same patients you refer to pulmonology – helpful to get a baseline prior to treatment
  - If you feel your patient has poor nutrition status, endocrine may be able to help
  - High risk population if you're considering EOS treatment – SMA, OI
  - DXA Z score < -2 in TBLH and/or lumbar spine

TREATMENT OF EOS WITH KNOWN POOR BONE HEALTH

- Nutrition
- Exercise/PT
- **Medications**
- **Surgery Modifications**

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MEDICATIONS

- "General" Bisphosphonate Indications
  - Multiple (typically 3) long bone fractures in 1 year
  - Compression fractures of the spine

As bisphosphonates inhibit bone turnover, they are going to be most effective for trabecular bone such as the spine

BISPHOSPHONATES → SCOLIOSIS PROGRESSION IN OI

- Retrospective review of spine radiographs of 437 patients with OI caused by COL1A1 or COL1A2 mutations → compared relationship btw OI, genotype, and response to bisphosphonate treatment
- 55% had scoliosis at final follow-up
  - 89% of Type 3; 61% of Type IV; 36% of Type 1
- During 1st 2-4 yrs of bisphosphonate treatment, patients with Type 3 OI had less progression than before bisphosphonate treatment
- In Type 1 and Type 4 OI, bisphosphonates did not change rate of progression

Sato et al. "Scoliosis in osteogenesis imperfecta caused by COL1A1/COL1A2 mutations." *Bone* 86 (2016) 53–57.

SCOLIOSIS IN OSTEOGENESIS IMPERFECTA

- Cause of scoliosis in OI
  - Bone fragility (vertebral fractures)
  - Ligamentous laxity – ligaments between the bones may not be able to hold the bones as stable
  - Possibly muscle weakness
- Rarely seen before age 6

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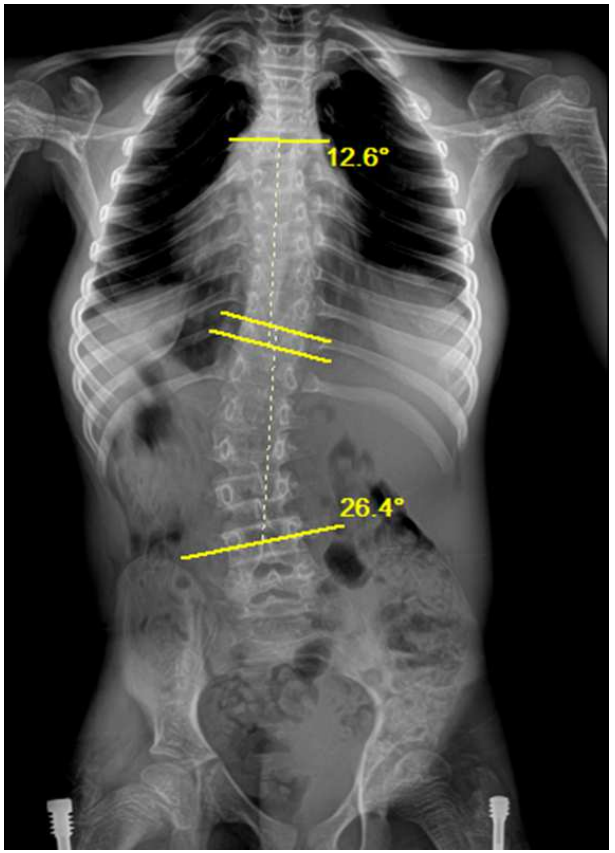
SCOLIOSIS

- Not every child with moderate/severe OI will develop scoliosis
- Medications like bisphosphonates may protective against scoliosis as they decrease VB fractures and improve the shape over time
- Bisphosphonates will also allow some of our children to ambulate which helps build protective core/ trunk strength

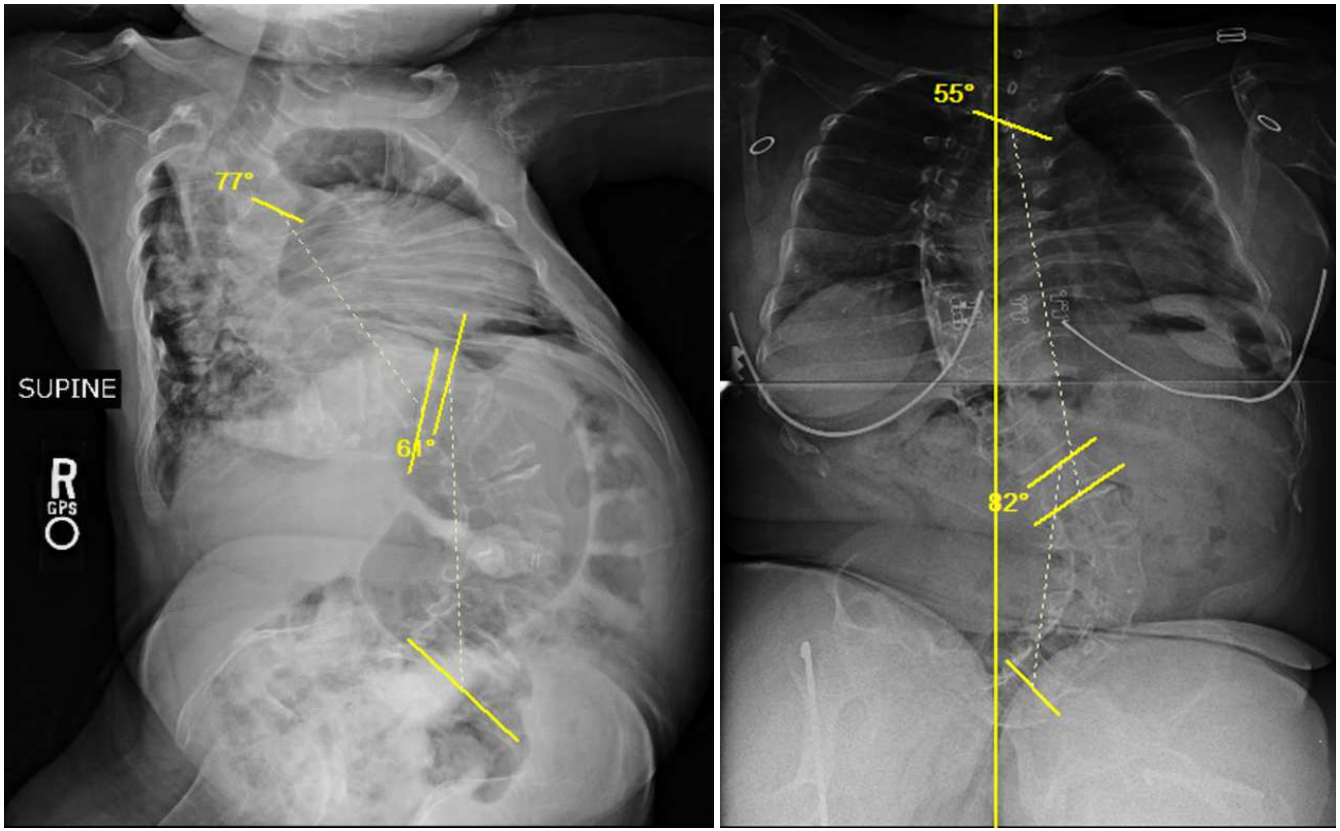
SCOLIOSIS TREATMENT

- In younger children, options include:
  - PT exercises
  - Aquatic therapy
  - Bracing ?
  - Casting (EOS) ?
  - Surgery: MCGR ?



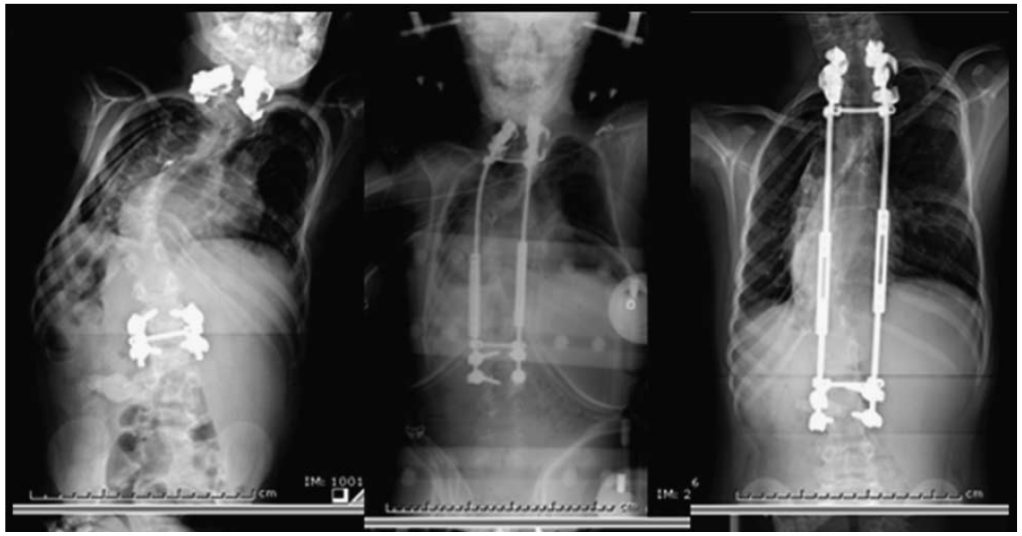
SURGICAL SCOLIOSIS TREATMENT

- For those with more moderate to severe OI, surgical indications are different and techniques change
  - Consider fixation for curves > 50 degrees, but bone needs to be strong enough to accept some type of hardware



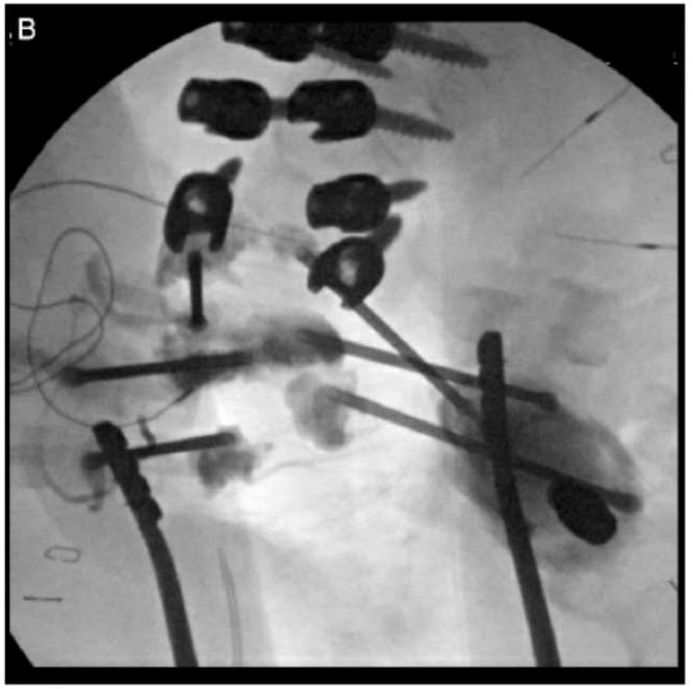
CHANGES IN SCOLIOSIS MANAGEMENT

TECHNIQUE 1 – STAGED PRE-IMPLANTATION WITH BONY ANCHORS



Gomez et al, *JPO*. 37(8), 2017.

TECHNIQUE 2 – PEDICLE SCREW CEMENT AUGMENTATION



O'Donnell et al, *JBJS* Reviews. 2017 5(7) e8

CONCLUSIONS

- Little is known about the specific relationship of bone strength and EOS
- Treatment likely alters the bone strength → however, the “trade” may be increased pulmonary function
- As we continue to “master” growing rod technologies, should focus on optimizing bone strength in addition to pulmonary function
- For our known syndromic/osteopenic populations, there are current methods to alter surgical techniques. May be opportunities in the future with implant design to decrease stress shielding?

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1. McCall et al. “Alterations in Vertebral Growth Following Prolonged Plaster Immobilisation.” *Acta Orthopaedica Scandinavica*. 52:3, 327-330.
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