Endocrine Fellows from the University of Colorado School of Medicine

- Kelsey DeSalvo
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Osteogenesis Imperfecta: Type III

Ken Tompkins, MD

Endocrinology Fellow
University of Colorado

History Of Present Illness

- 32 yo woman presents to endocrine clinic to discuss therapy for OI
- Diagnosed at birth; no antenatal indications but born with severe deformity of lower limbs, soft skull
- No genetic testing in childhood; diagnosed clinically with Type 3 OI
- Innumerable fractures in childhood
  - Unable to bear weight on legs, immediate fracture when attempts
  - Transported on a pillow by her parents as child, would fracture if she slid off pillow and parents tried to place her back
- No issues with dentition; had braces, tolerated fine
- Last fracture was about 4 years ago, after fall out of power wheelchair

Relevant Medical History

- Past Medical History
  - Restrictive lung disease, on supplemental O2
  - Hypophosphatemia
  - Nephrocalcinosis
  - Chronic Pain Syndrome
  - Asthma, gets pred bursts 1-2x/year
  - Normal menstruation

Soc Hx

- Never tobacco user
- Drinks socially 1-2x/year
- No marijuana or illicit drug use
- Previously worked in customer service, now disabled

Family History

- No family hx of osteogenesis imperfecta or easy fracture
- No family hx of osteoporosis

Meds:

- Albuterol
- Duloxetine
- Fluticasone/Salmeterol
- Gabapentin
- Extended-release Morphine
- Oxycodone
- Sertraline
- Ethinyl-estradiol/norgestimate

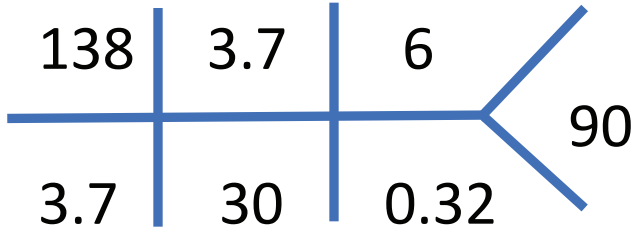
Previous Treatment History

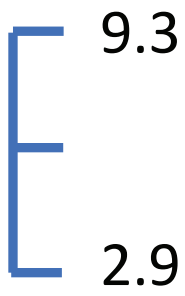
- Received alendronate ages 16-18 as part of a clinical trial
- Given dose of zoledronic acid in 2014
- Never followed up after this, noncompliant due to psychosocial issues

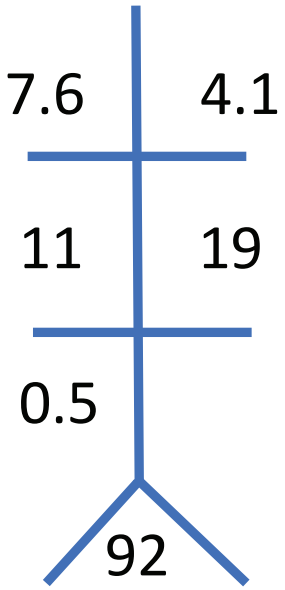
Physical Exam

- Vitals: Reported Ht 3’6”, unable to get weight; BP 96/60
- General: **Very short stature**; significant kyphoscolosis; in power wheelchair
- HEENT: **Fair dentition, no significant caries**, appears to have all her teeth
- Eyes: **Mildly grey sclera**
- Neck: Thyroid not enlarged
- CV: RRR, no m/r/g
- Resp: CTAB, no w/r/c
- MSK: Markedly limited ROM of b/l arms at shoulders, elbows; marked clinodactyly; significant kyphosclosis on palpation of spine

Relevant Data







PTH 34

25-OH Vitamin D 24

CTX 72

Imaging:

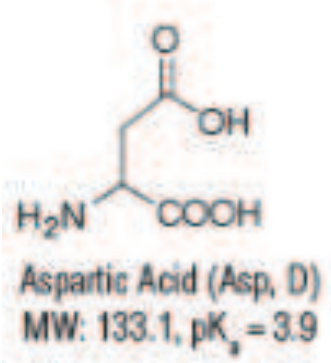
No Recent BMDs

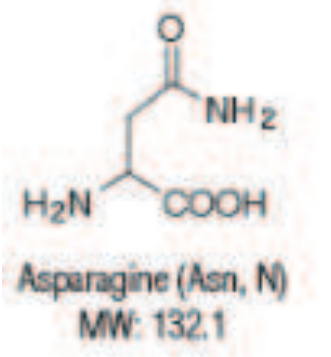
MRI T-Spine January 2018:

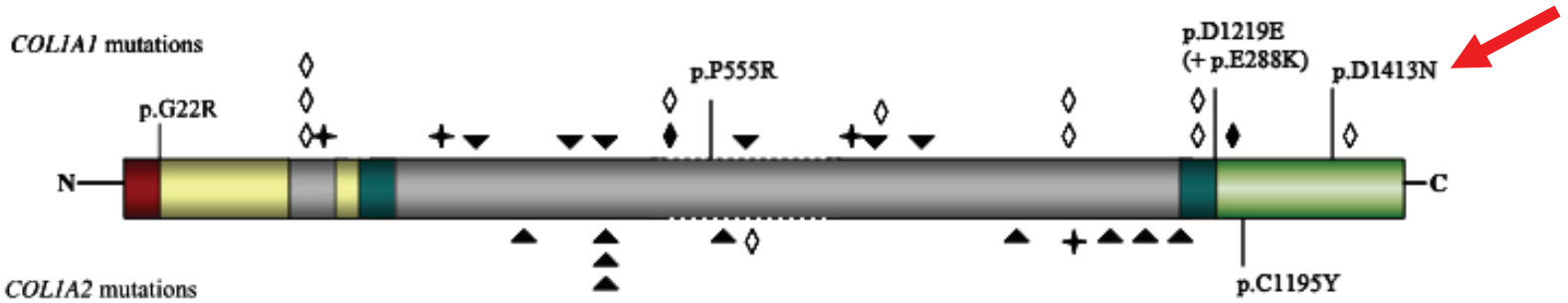
- Advanced rotary dextroscoliosis
- Small chronic compression fracture T2, T3; large compression fx T4-T12

Genetic Testing

- Given presence of other metabolic abnormalities (low phos, nephrocalcinosis), recommended genetic testing
- DNA sequencing showed a guanine → adenine point mutation at nucleotide 4237 of COL1A1 Gene
- Substitutes asparagine for aspartic acid in c-terminal domain
- This mutation previously identified in a patient with Type II OI







R Pollit. Human Mutation. March 2006

Questions for Discussion

- Last fracture occurred after she received zoledronic acid. Is this a treatment failure?

- Is there a role for other therapies besides bisphosphonates?

Osteogenesis Imperfecta

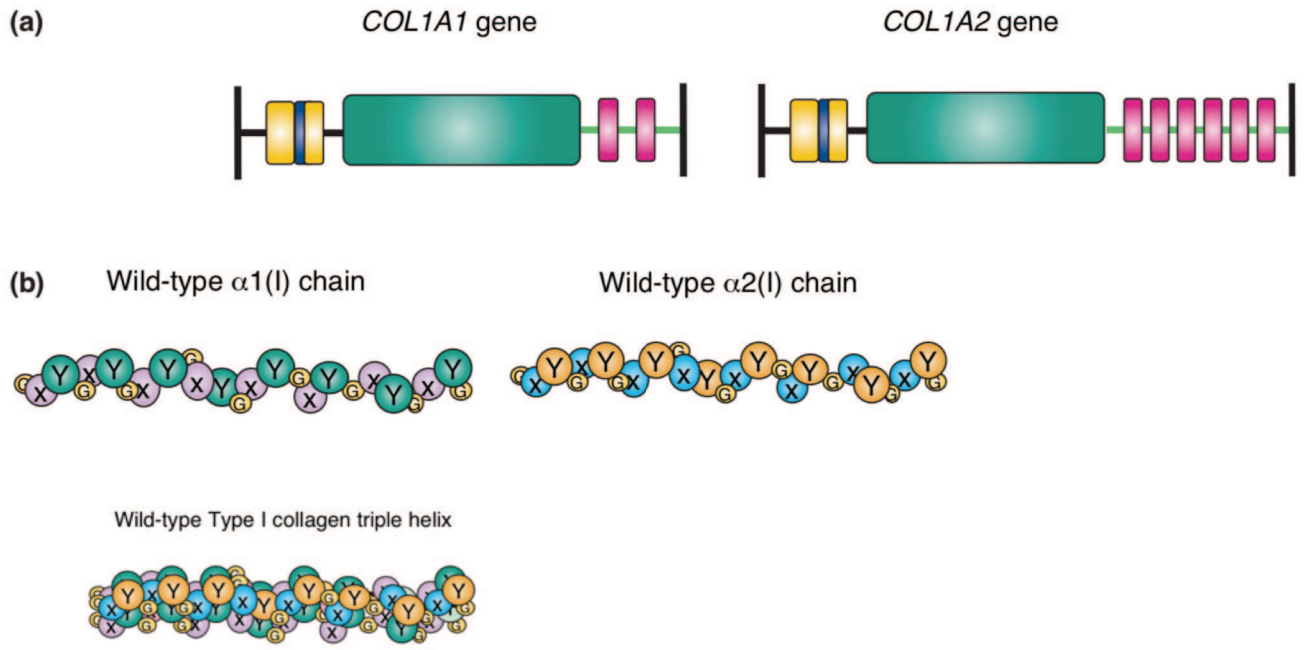
- Heritable bone disorder characterized by bone fragility and decreased bone mass
- Mutation affecting Type 1 Collagen formation
- Phenotype can range from easy fracture to severe deformity and organ abnormalities
- Classically characterized by Sillence Criteria as phenotypes Types I-IV, with additional types based on new phenotypes, mutations

Type	Phenotype	Genetics	Mechanism
I	Non deforming, blue sclera, easy fracture	Autosomal dominant	Decreased COL1A1 production, *quantitative* defect
II	Severe deformity, pulmonary hypoplasia, fatal in childhood	Autosomal dominant, recessive De Novo	Amino acid substitution causing abnormal folding and aggregation of Type 1 Collagen, *qualitative* defect
III	Severe deformities, survive to adulthood	Autosomal dominant, recessive, De Novo	
IV	Moderately severe OI with normal sclera	Autosomal Dominant	

A Biggins et al. Current Osteoporosis Reports; September 2014: 279-288.
V Dijk et al. Osteogenesis Imperfecta: Clinical Diagnosis, Nomenclature and Severity assessment. American Journal of Medical Genetics

Pathogenesis of Osteogenesis Imperfecta

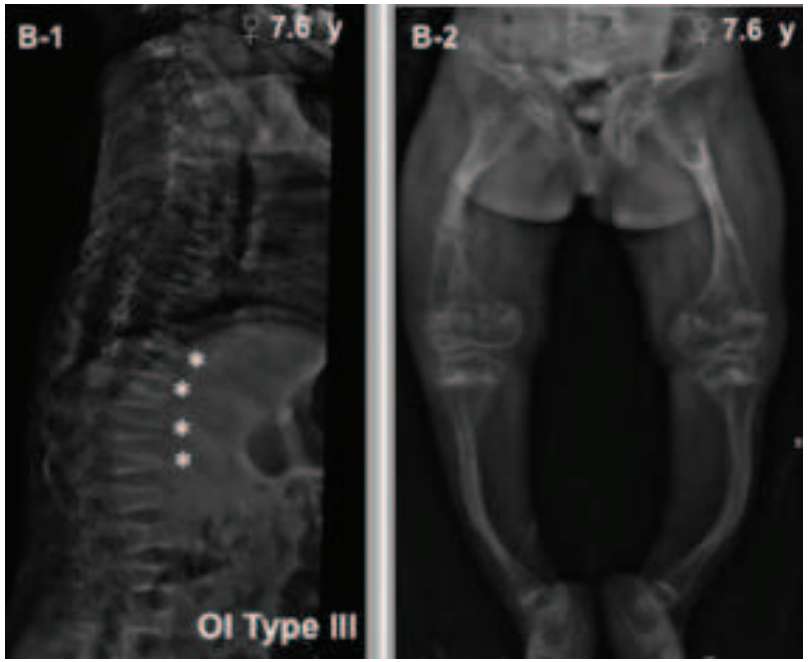
- Defects due to impairment in Type 1 Collagen aggregation, processing, secretion
- Mutations in *COL1A1/2* or enzymes involved in posttranslational processing lead to OI



N Fedarko et al. Osteogenesis Imperfecta. A Translational Approach to Brittle Bone Disease. 2014: 45-56

Type 3 Osteogenesis Imperfecta

- Usually due to glycine substitution in COL1A1 that leads to abnormal collagen folding and bone formation
- Characterized by short stature, osteopenia/fracture noted at birth, very early childhood, progressive skeletal deformity
- Blue sclera, hearing loss, dentogenesis imperfecta may or may not be present



T Paloma et al. Current Opinions in Endocrinology. December 2017.

Bisphosphonates in OI

- Bisphosphonates have been mainstay of treatment for OI for years

- Large RCT of 139 patients with OI, including 32 type III patients treated with alendronate:
  - Increases in L spine BMD
  - Decreases in bone turnover markers
  - No change in fracture rate at 2 years

- One controlled trial of 18 children with Type III and IV OI treated with IV pamidronate showed:
  - Increases in L spine BMD
  - Decreased UE fracture

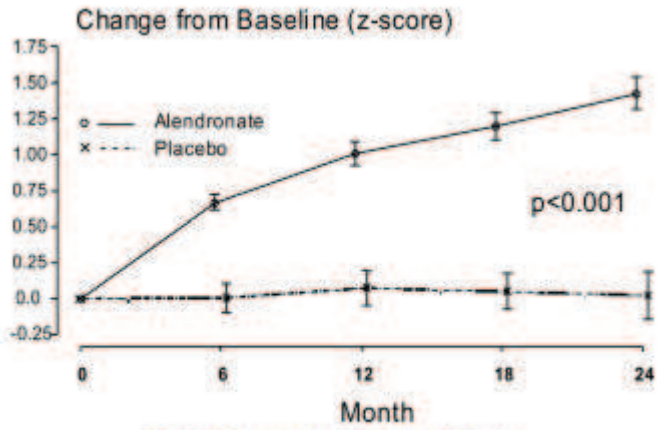


FIG. 2. Change in LS (L1–L4) areal BMD.

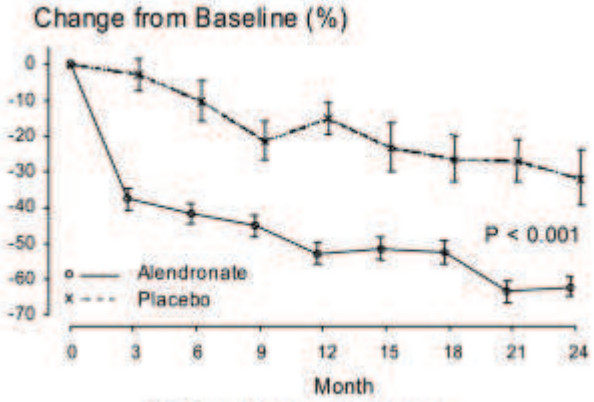
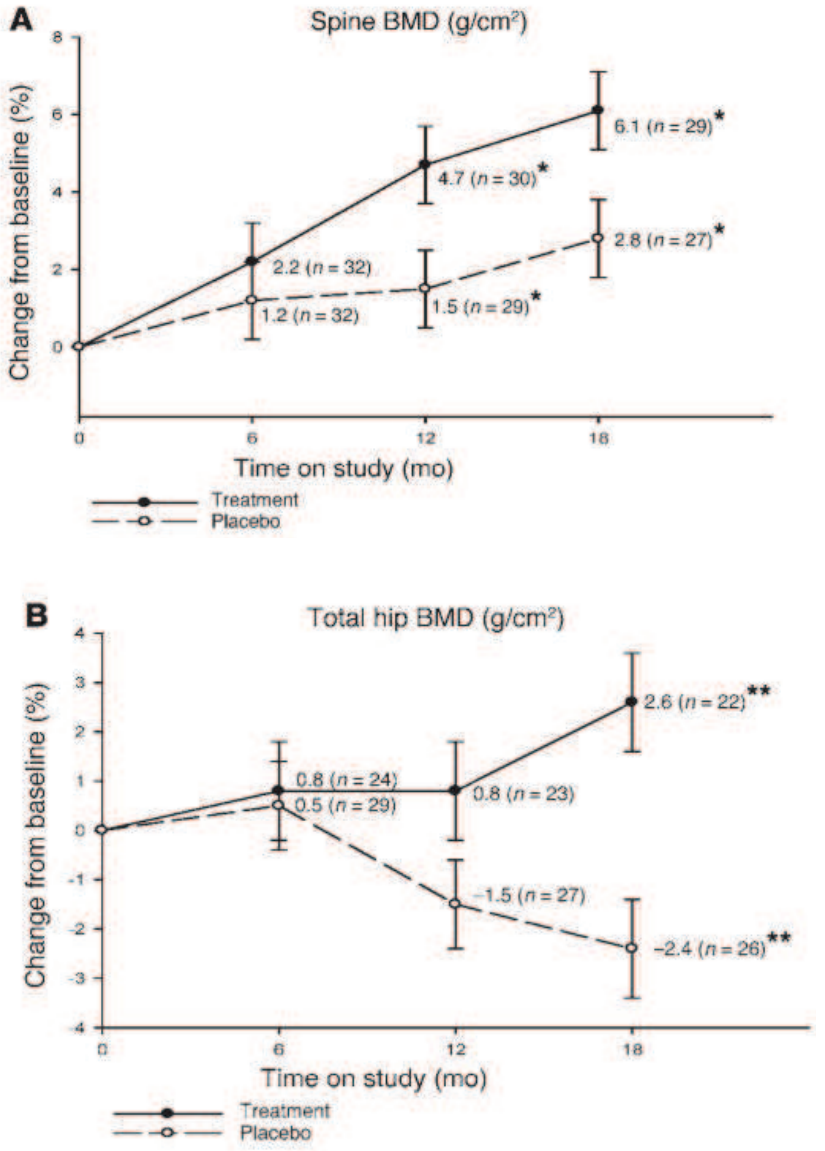


FIG. 4. uNTx to creatinine ratio.

L Ward et al. JCEM, 2011 (2): 355-364.
A Letocha et al. JBMR, 2005 (20): 977-986

Teriparatide in OI

- Teriparatide stimulates bone remodeling and formation, role in OI?
- RCT of 78 patients with OI, including 14 type III and 12 type IV OI patients:
  - Increased Spine BMD
  - Increased Total hip and Fem Neck BMD
  - Increased spine QCT scores
  - Increased bone formation markers
- But…
  - Subgroup analysis showed patients with type III/IV had changes in BMD similar to placebo
  - P1NP did increase in III/IV but not as significant as type I



E Orwoll et al. JCI 2014; 124 (2): 491-498

Questions For The Panel

- Would you consider the fact that she fractured on zoledronic acid a treatment failure?

- Would you consider teriparatide in her?

QUESTIONS/COMMENTS?

Thank You!

A CASE OF TOOTH RESORPTIVE DISORDER AND OSTEOPOROSIS

Adnin Zaman, MD

University of Colorado

Annual Metabolic Bone Disease Society Meeting

DISCLOSURES

None

HISTORY OF PRESENT ILLNESS

- 65 yo F with tooth resorptive disorder (TRD) and osteoporosis since her 40s with a recent L1 fracture presented for advice on osteoporosis treatment
- Osteoporosis diagnosed in 1990s by dentist who discovered 8 resorptive teeth
- DXA in 1998 revealed low BMD
  - Given alendronate but patient self-discontinued; switched to HRT
  - Poor nutrition and low body weight at time of diagnosis
- Good dental care in youth
  - Had severe overbite with multiple years of braces
- No problems with hearing or vision
- Multiple fractures in the past, due to trauma

HISTORY OF PRESENT ILLNESS

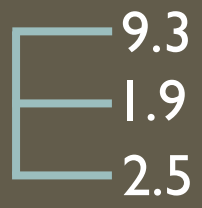
- **Allergies:** Codeine
- **Home Meds:** Estradiol 0.5mg Daily, Ergocalciferol, Progesterone 200mg QHS
- **PMHx:** anxiety, depression, **L1 vertebral fracture, osteoporosis, tail bone fracture, T11 vertebral fracture, thumb fracture, tibia/fibula fracture, toe fracture x2, tooth resorption**
- **PSHx:** multiple oral cavity surgeries, including root canals
- **FHx:** mother – **osteoporosis/hip fracture (age 94),** bladder cancer; father – heart attack
- **SHx:** **tobacco – >75 pack-year smoking history**; alcohol – 2 glasses of wine per week; drugs – none

PHYSICAL EXAM

VITALS: BP 129/76, HR 80, Ht 5'4", Wt 60.3kg, **BMI 22.83**

- **General:** A/O x3, well developed and well nourished, no acute distress
- **HEENT:** NCAT, clear oropharynx, **wearing dentures on 10 teeth but missing 14 teeth overall,** normal gums, EOMI, PERRL, **normal sclera,** no icterus, normal neck range of motion, supple, no tracheal deviation, no thyromegaly. No cervical LAD
- **CV:** RRR, no m/r/g
- **Resp/Pulm:** normal effort, CTAB, no w/r/c
- **Abd:** soft, NTND, no rebound or guarding
- **MSK:** normal range of motion, no deformities, **no hyper-flexibility**
- **Neuro:** alerted to person, place, and time. Normal reflexes

LABS (5/2018)

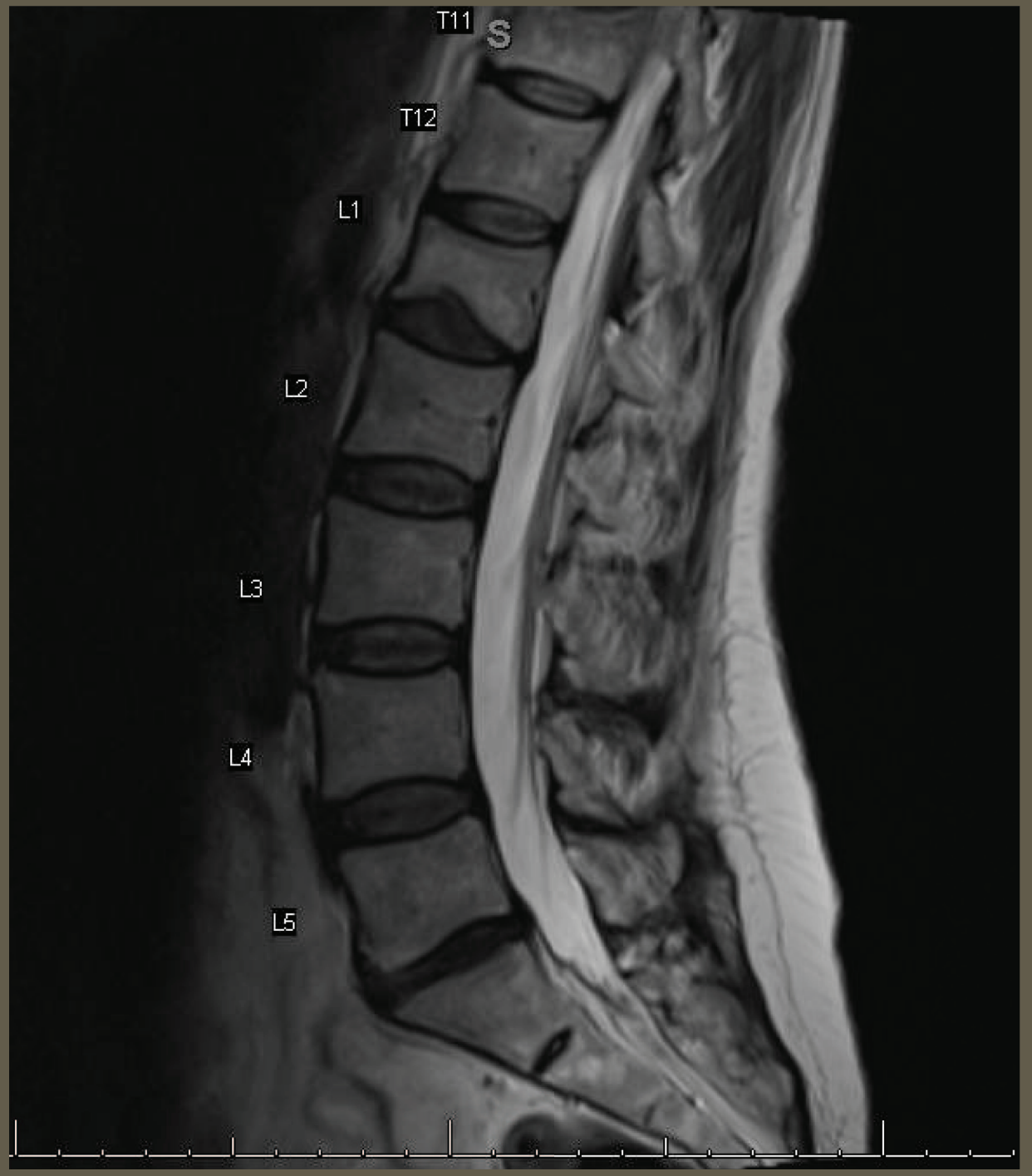


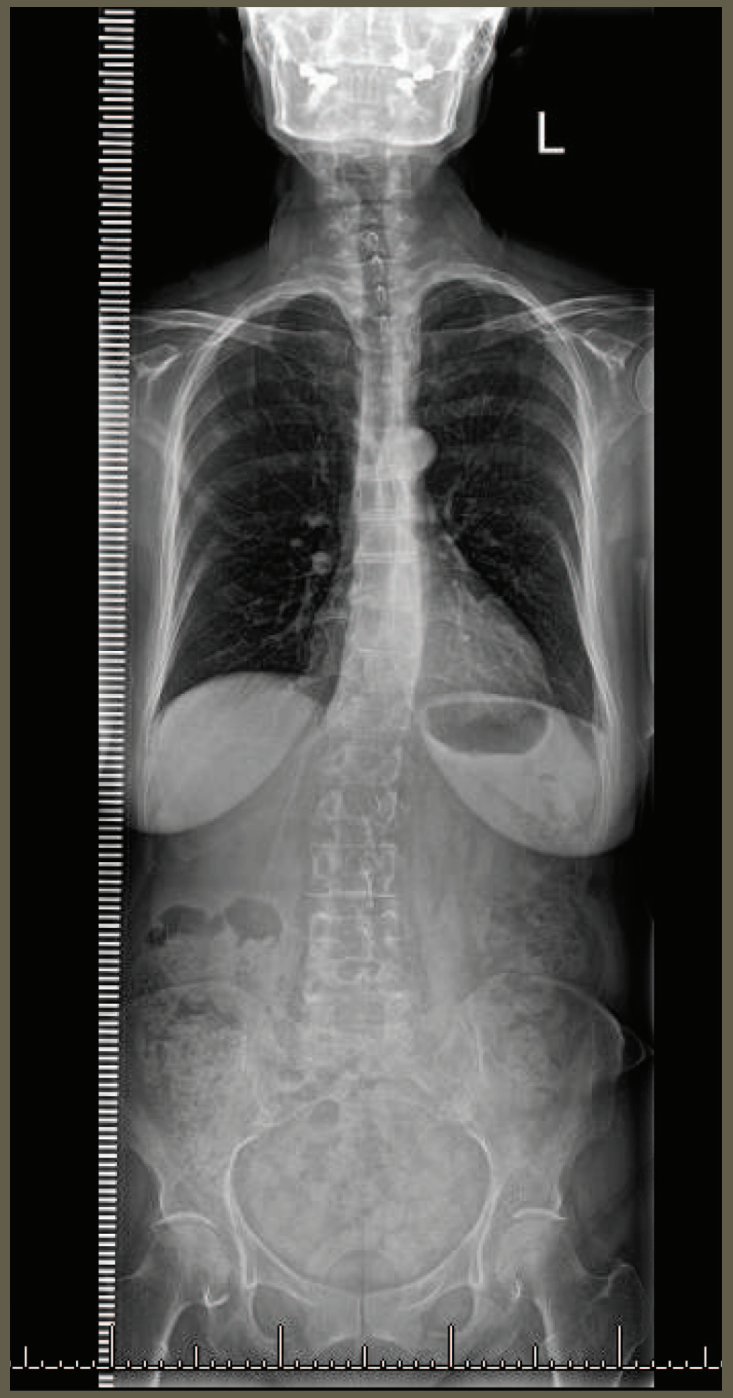
24 hour calcium 135
PTH 55
SPEP/UPEP not detected
Anti-TTG Ab <4.0
Vitamin D 24 → 89
TSH 0.92
HgA1c 5.5%
Total cholesterol 184, TG 76, **HDL 64,** LDL 106

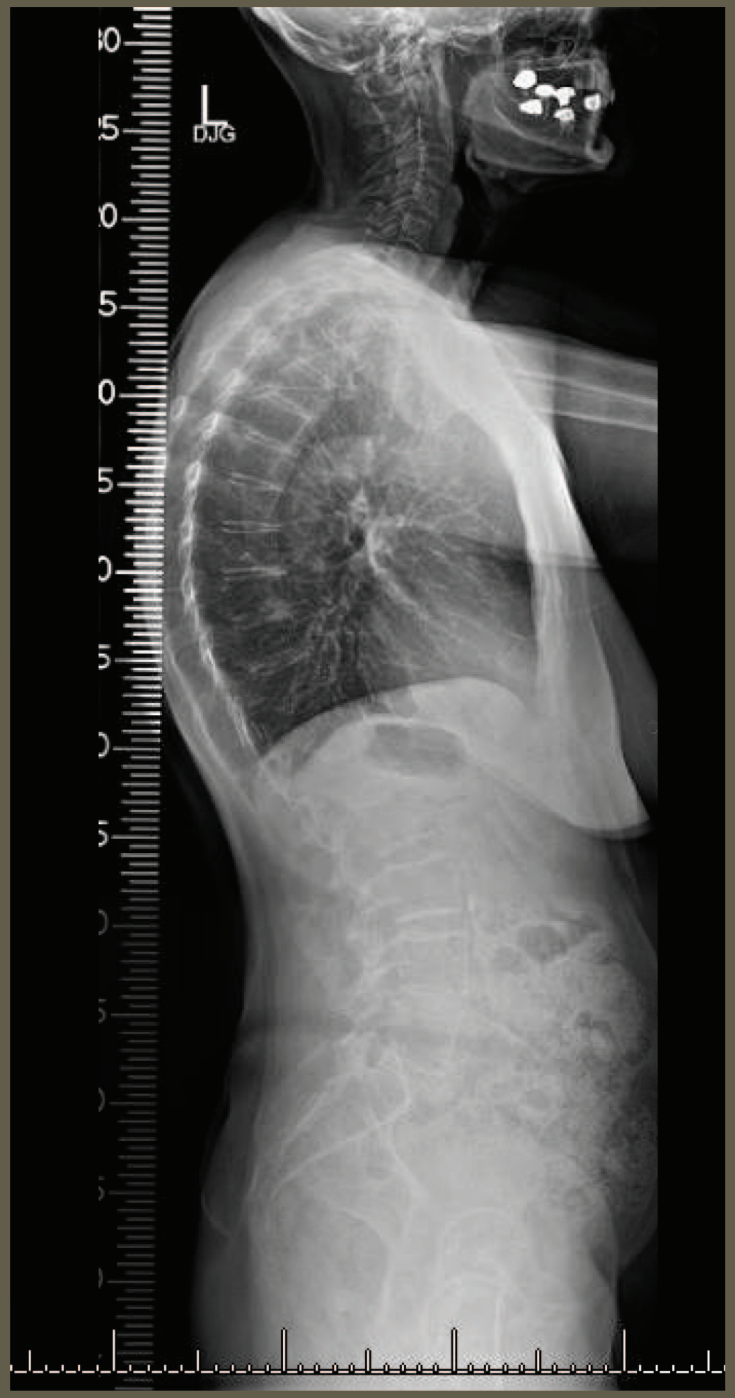
IMAGING: MRI (10/2017)

MRI L-Spine without contrast (10/19/17):

- 1. Subacute superior endplate compression fracture of T11 with mild retropulsion partially visualized. There are no findings to suggest significant central canal stenosis.
- 2. Mild chronic anterior wedge deformity of L1 unchanged.
- 3. Lumbar spondylosis resulting in mild foraminal stenosis without significant narrowing of the central canal.



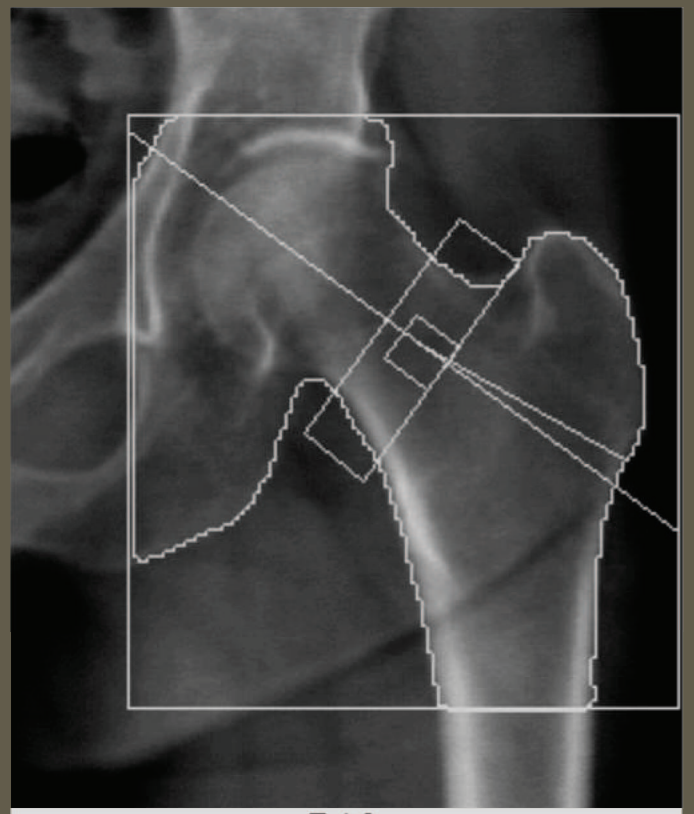


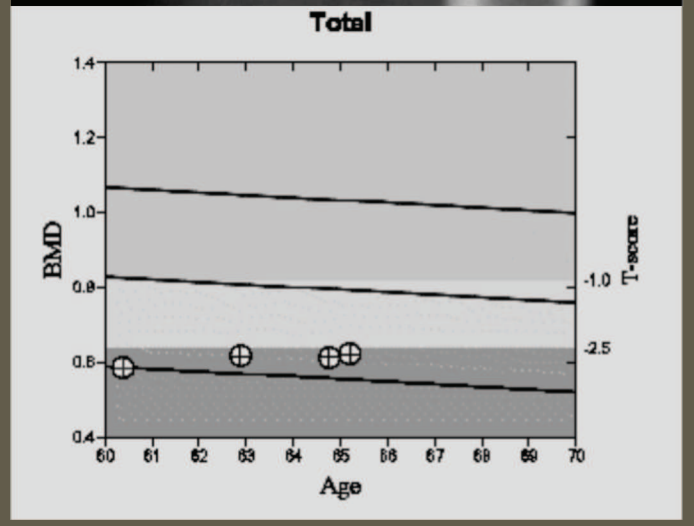


IMAGING: XRAY (4/2018)

X-Ray Muscle Compare (4/12/18):

- Compression fracture L1 with approximately 30% loss of height
- Compression fracture at T11 with 25% loss of height
- Minimal changes from images obtained November 2017
- Degenerative spondylolisthesis in L4-L5
- Thoracic maximal kyphosis
- Comparison lumbar spine obtained October 2016 shows compression fracture at L1

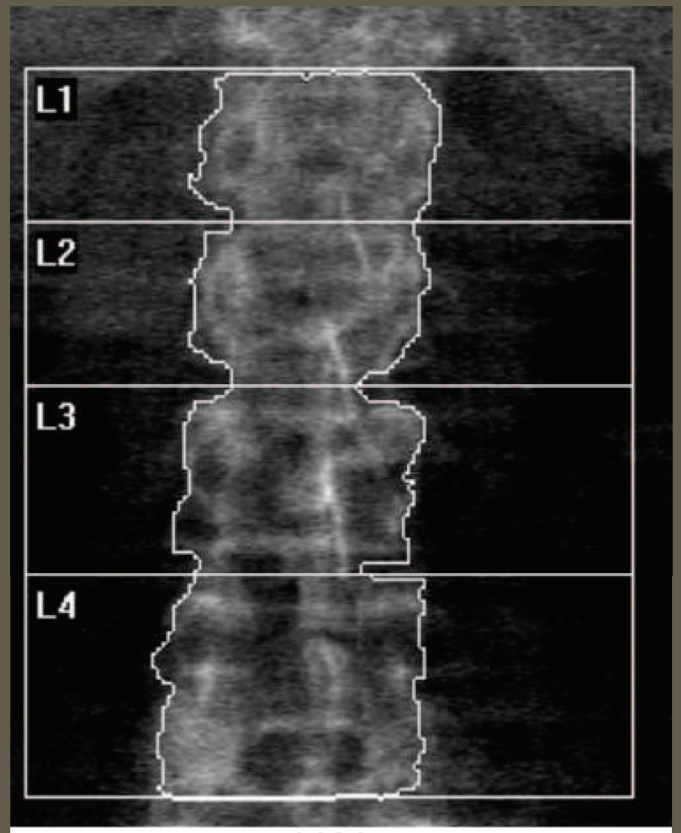


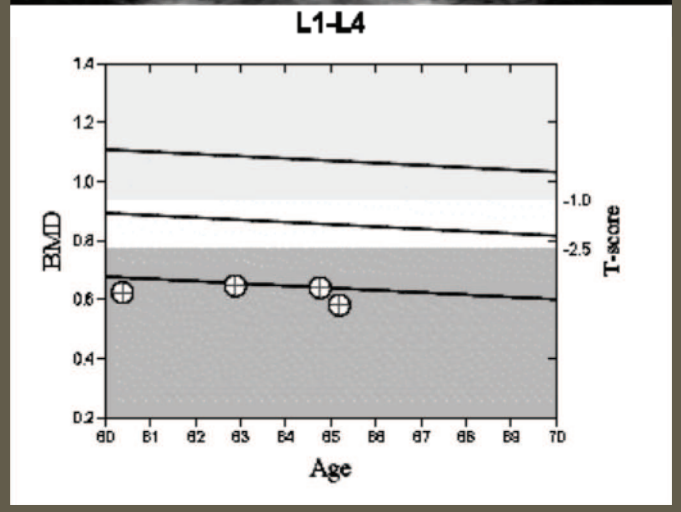


COMPARING DEXA SCANS: HIPS

Region	Area [cm²]	BMD [g/cm²]	T-score	Z-score
Neck	5.10	0.482	-3.3	-1.8
Troch	10.66	0.431	-2.7	-1.6
Inter	19.89	0.760	-2.2	-1.2
Total	**35.66**	**0.622**	**-2.6**	**-1.4**

Region	Scan Date	Age	BMD	T-score	BMD Δ vs. baseline	BMD Δ vs. previous
Total	4/2018	65	0.622	-2.6	-0.028 (-4.3%)	0.009 (1.5%)
	12/2015	62	0.618	-2.7	0.033 (5.6%)	0.033 (5.6%)
	*8/1998	45	0.65	-2.4		
Neck	4/2018	65	0.482	**-3.3**	**-0.13 (-21.2%)**	-0.015 (-3.0%)
	12/2015	62	0.498	-3.2	0.019 (3.9%)	0.019 (3.9%)
	*8/1998	45	0.612	n.m.		



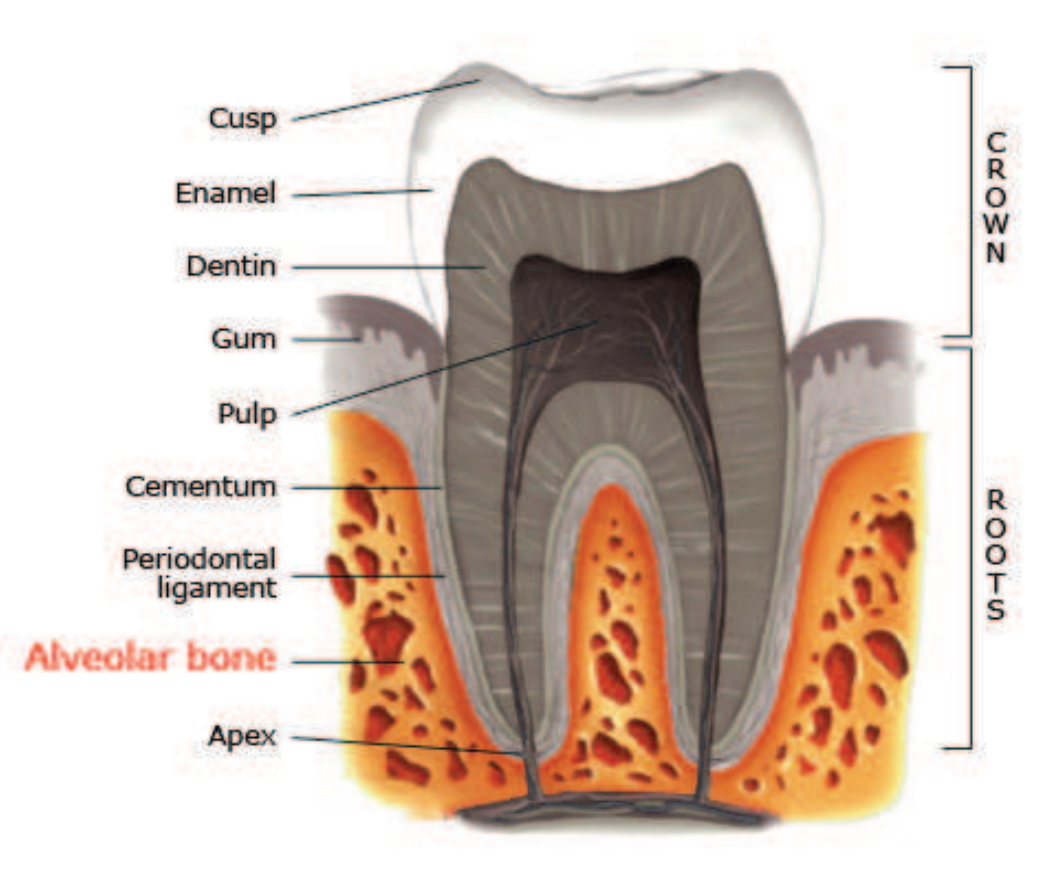


COMPARING DEXA SCANS: L-SPINE

Region	Area [cm²]	BMD [g/cm²]	T-score	Z-score
L1	12.08	0.624	-3.3	-1.8
L2	12.54	0.638	-3.5	-1.8
L3	15.12	0.595	-4.4	-2.6
L4	20.72	0.514	-5.0	-3.1
Total	**60.46**	**0.582**	**-4.2**	**-2.5**

Scan Date	Age	BMD	T-score	BMD Δ vs. baseline**	BMD Δ vs. previous
4/2018	65	0.582	**-4.2**	**-0.043 (-7.0%)**	-0.058 (-9.1%)
12/2015	62	0.645	-3.7	0.020 (3.2%)	0.020 (3.2%)
**7/2013	60	0.625	-3.8	-0.169 (-21.3%)	-0.108 (-14.7%)
6/2014	51	0.733	-2.9	-0.061 (-7.8%)	0.061 (-7.8%)
*8/1998	45	0.794	-2.3		

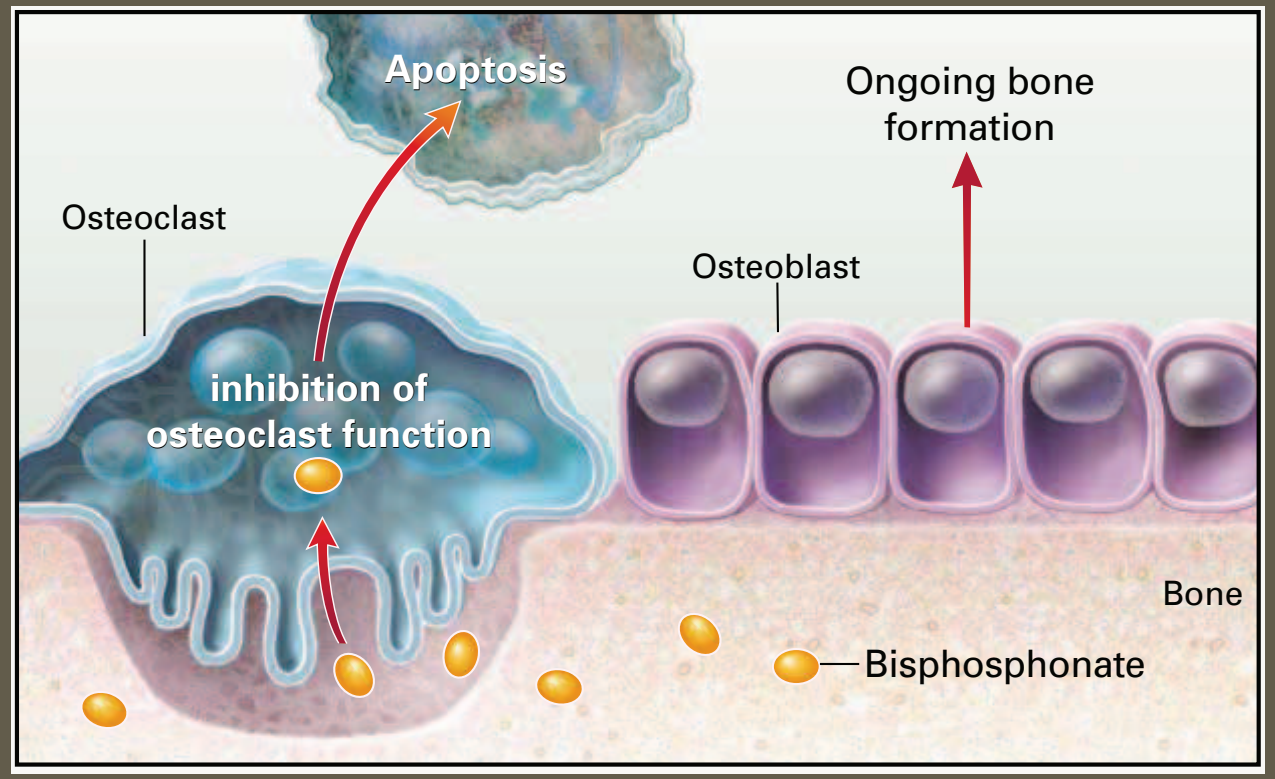
TOOTH RESORPTIVE DISORDER



- Loss of alveolar bone is the most important feature of periodontal disease
- Alveolar bone loss may be related to generalized bone loss due to dietary calcium deficiency (in dogs)
- Protective layers above the alveolar bone minimize resorption, so extensive trauma may be needed
- Multiple older studies, looking at osteoporosis and residual ridge resorption
- Resorption likely due to osteoclastic overactivity

Krook et. al. 1971 | Trope. 2002

BISPHOSPHONATES AND MECHANISM

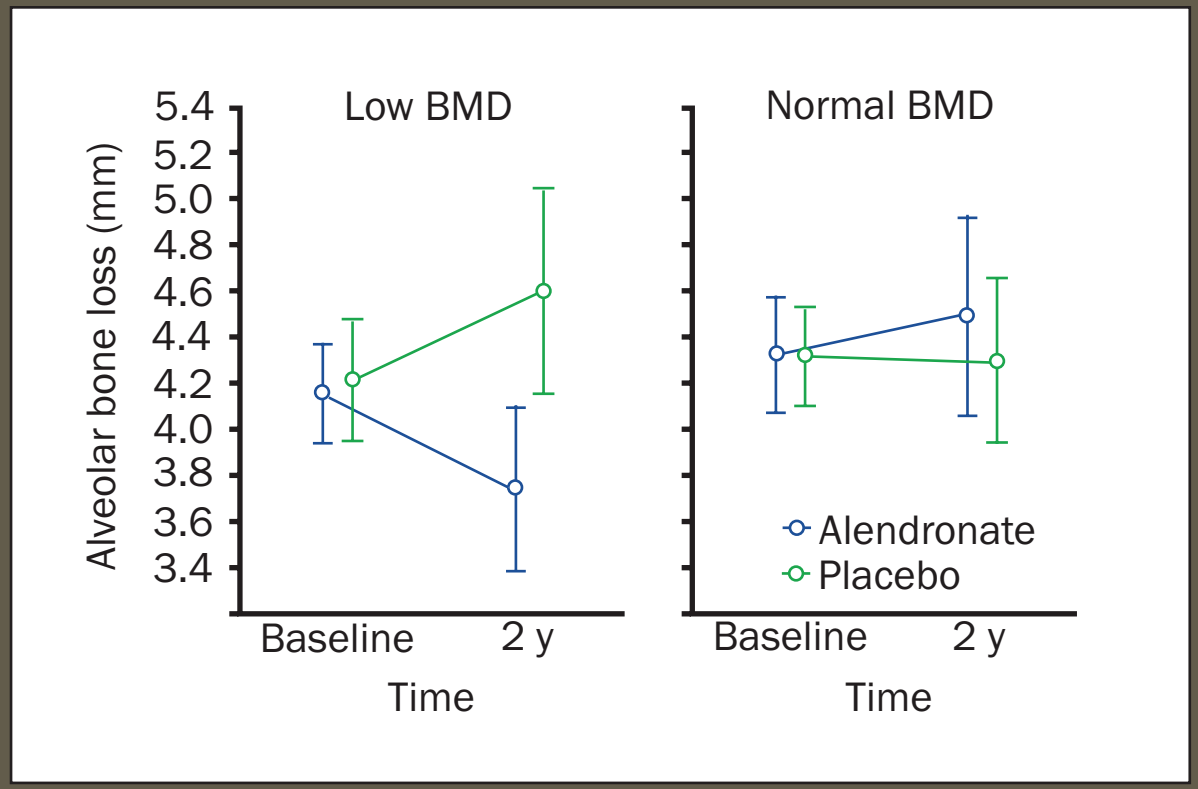


- Bisphosphonates are chemically absorbed into bone, decrease osteoclast number and activity, and thereby decrease bone resorption

Solomon, 2002.

SAFETY OF ORAL BISPHOSPHONATES: CONTROLLED STUDIES ON ALVEOLAR BONE

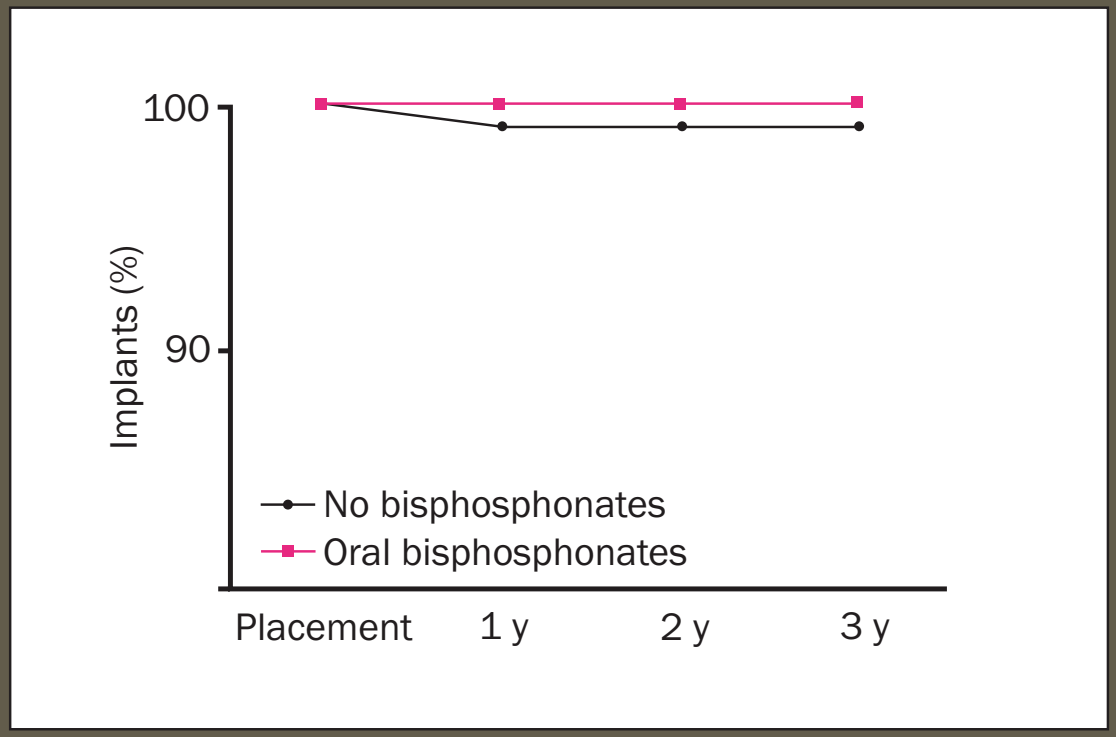
- Study 1
  - 335 patients with moderate or severe periodontal disease randomized to placebo or 70mg alendronate once weekly
  - Alveolar bone height were assessed over 2 years
- Results
  - No cases of ONJ with **lower incidences of infection and tooth loss** in alendronate group



Jeffcoat, 2006.

SAFETY OF ORAL BISPHOSPHONATES: CONTROLLED STUDIES ON ALVEOLAR BONE

- Study 2
  - Single-blind controlled study looking at implant success in 50 consecutive patients (210 implants)
  - 25 patients received bisphosphonate and 25 age-matched controls
  - Implant safety and success, rates of ONJ were observed
- Results
  - No cases of ONJ in either group and implant success >99%



Jeffcoat, 2006.

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QUESTIONS?

Thank you!

A CASE OF XLH

CASE: 72 YO FEMALE WITH HX OF XLH

Bone History

- Seen as a child at Shriner's St Louis for low serum phos and rickets
- Bilateral tib/fib ostomy age 8 and 15
- Very poor dentition with failed implants and she now has dentures
- Endorses bone pain localized to L fibula, fatigue, and hearing loss. She denies any falls/ fractures

Family History

- Known family h/o XLH (grandmother, mother and brother).
- Has one child, unaffected

TREATMENT HISTORY

- Po phosphorus and Vitamin D as a child. Not treated with GH
- No treatment from age 30 to 67
- At age 67, started on calcitriol 0.25mcg BID, D3 1000 IU daily, and neutraphos 250mg TID
- Tried various doses of Calcitriol and Phosphorus, however pt with persistent elevated alk phos, elevated PTH and bone pain
- Trialed Cinacalcet, however developed hypocalcemia
- Current Regimen: Calcitriol 0.25mcg BID and KPhos 1000mg BID

EXAM

- BMI 21.98, Height: 4’ 10.5,” BP 140/78
- + Bowed legs. No kyphosis
- Strength grossly normal, no trouble standing from seated, cautious gait

DATA:

UCH Labs:

5/2018: Calcium 9.5, Phos 1.5, PTH 104, Alk Phos 109, Vitamin D 25 25, Vitamin D 1, 25 41

OSH Labs:

9/2015: Calcium 8.7, phos 2.1, Alk phos 174, PTH 156, Urine Calcium 91.5 mg/24 hr

7/2013: Calcium 8.8, phos 2.0, Alk phos 173, PTH 150, Urine Calcium 121.6 mg/ 24 hr, Vitamin D 25 30

Imaging:

Normal Renal ultrasound

CASE DISCUSSION

- What is XLH?

- Are there any new treatment options?

HYPOPHOSPHATEMIC RICKETS

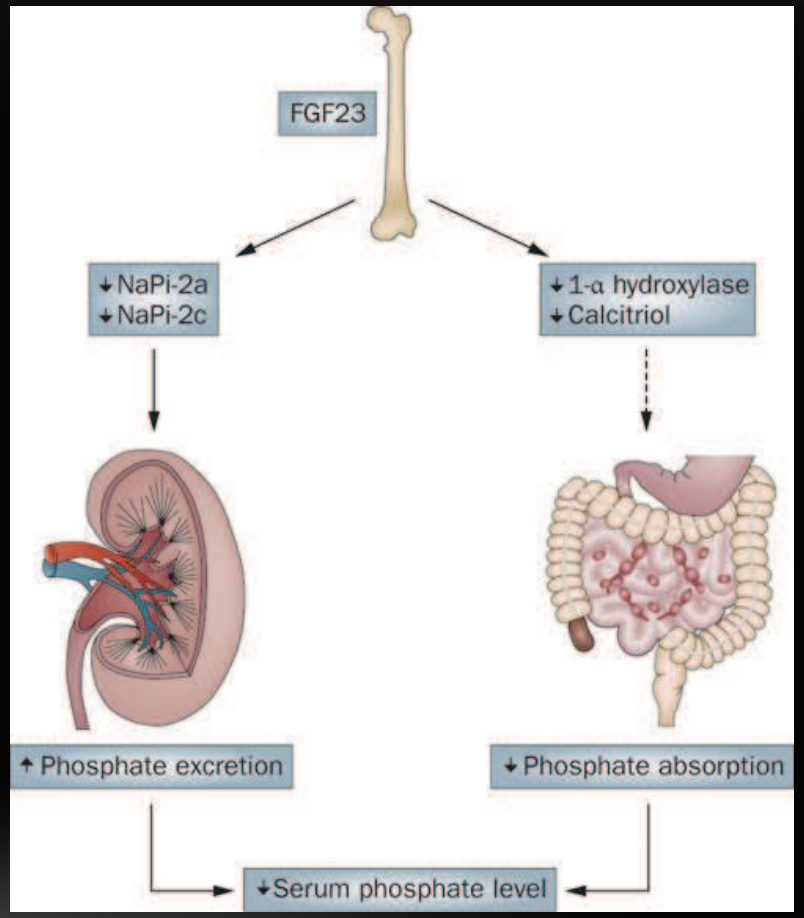
Hypophosphatemia		
FGF23-mediated	Gene	mutation
X-linked hypophosphatemia (XLH)	PHEX	LOF*
Autosomal dominant hypophosphatemic rickets (ADHR)	FGF23	GOF*
Autosomal recessive hypophosphatemic rickets 1 (ARHR1)	DMP1	LOF*
Autosomal recessive hypophosphatemic rickets 2 (ARHR2)	ENPP1	LOF*

- XLH is a X linked dominant disease
- 1/20,000 live births
- Most common form of hypophosphatemic rickets

Carpenter, Thomas, Primary Disorders of Phosphate Metabolism. Endotext.org, Accessed 10/1/2018

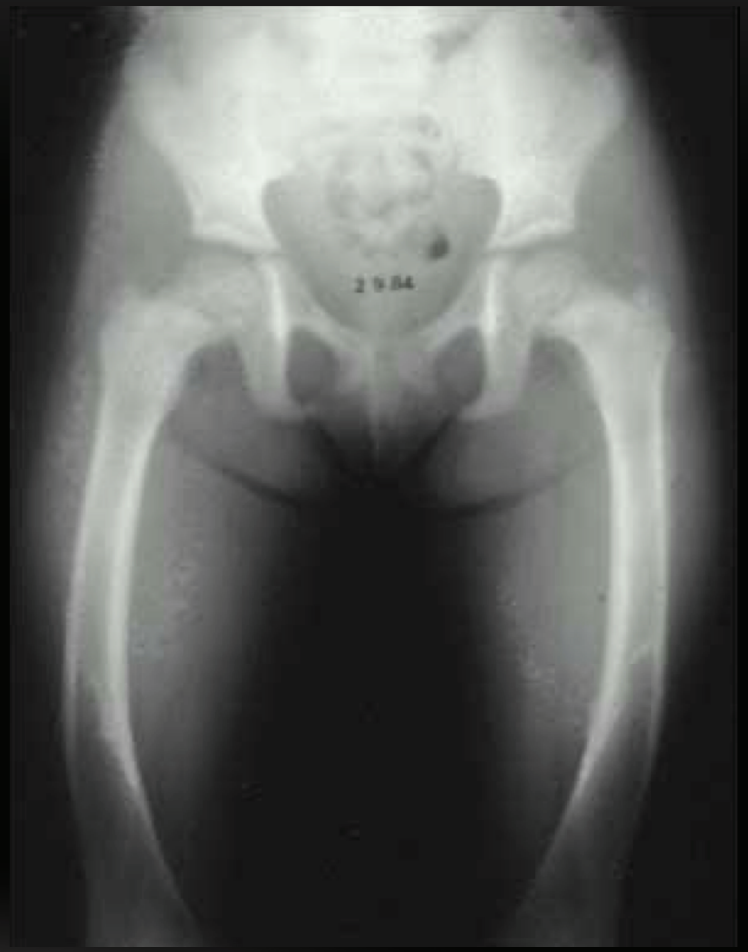
XLH: LOSS OF FUNCTION PHEX GENE

- Unclear exact mechanism
- Results:
  - Increased FGF23 (fibroblast growth factor 23)
  - Decreased renal phosphate reabsorption
  - Low serum phosphorus
  - Normal Calcium
  - Normal to elevated PTH
  - Normal serum 25 (OH) D
  - Decreased serum 1,25 $(OH)_2D$



CLINICAL OUTCOME

- Mild to severe bone disease
- Growth retardation and osteomalacia/rickets
- Limb deformities (bowing, knock knee), waddling gait
- Xray: non mineralized cartilage in epiphyseal regions
- Delayed denition and dental abscesses
- Bone pain as adults, arthritis and osteophytes
- Fractures and pseudofractures



Carpenter, Thomas, Primary Disorders of Phosphate Metabolism. Endotext.org, Accessed 10/1/2018

TREATMENT

Conventional Therapy

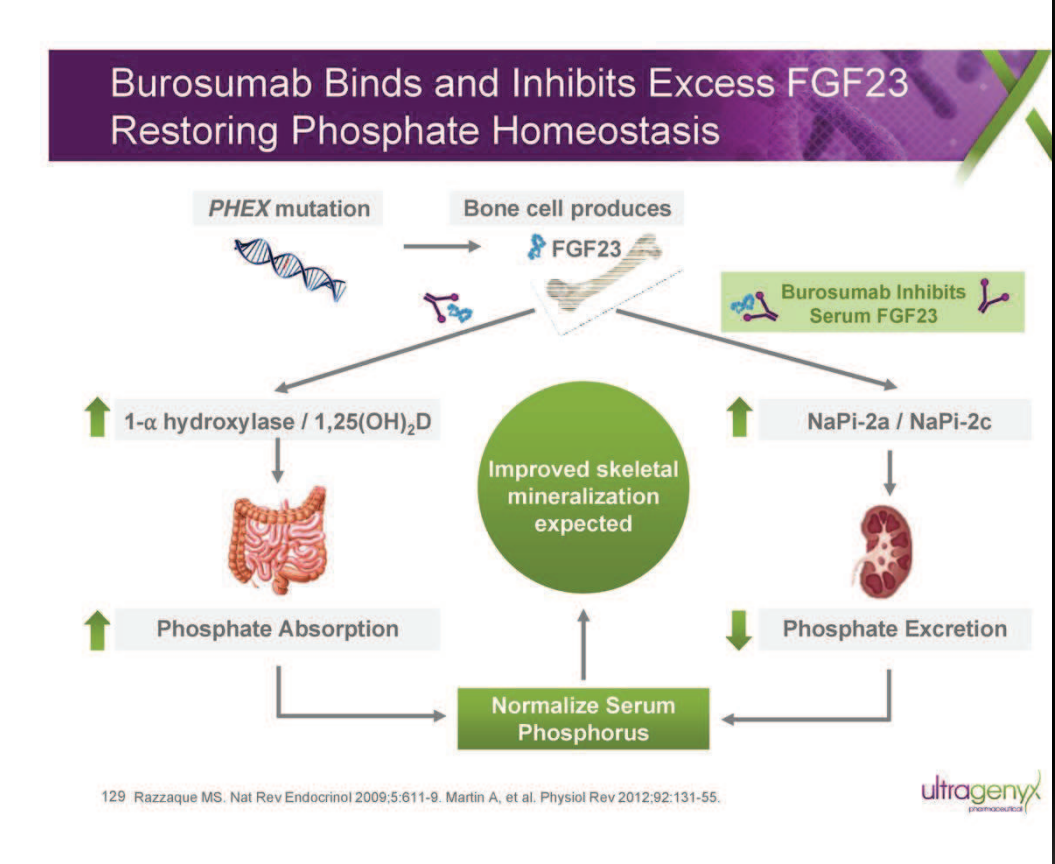
- Calcitriol: 20-50 ng/kg/day, BID dosing, max 3 mcg
- Phosphorus: 20-75 mg/kg/day, max 2.5 grams

- Toxicities: hypercalcemia, hypercalciuria, nephrocalcinosis, decreased GFR
- Reduced effect on growth

New Alternative

- Burosumab: monoclonal antibody to FGF23

BUROSUMAB



- Pediatrics: 0.8 mg/kg subq q 2 weeks, titrate
- Adults: 1 mg/kg subq q 4 weeks, titrate to max dose 90 mg q 4 weeks

ADULT INDICATIONS TO USE BUROSUMAB?

- 24 week RTC with symptomatic adults with XLH
  - Normalized serum phosphorus
  - Improved stiffness
  - Higher rate of fracture healing (43% vs 8% placebo) (however fractures were asymptomatic)
- But…
  - High cost
  - Unknown effect on fracture prevention
  - Symptoms of hypophosphatemia variable, some patients asymptomatic, treating lab values?

BACK TO CASE

- Patient asks about trying Burosumab
- Considerations for treatment: Pt with continued bone pain. Consider skeletal survey to evaluation for fractures and pseudofractures?

- What do you say?