

Fractures and Osteopenia in Rett Syndrome

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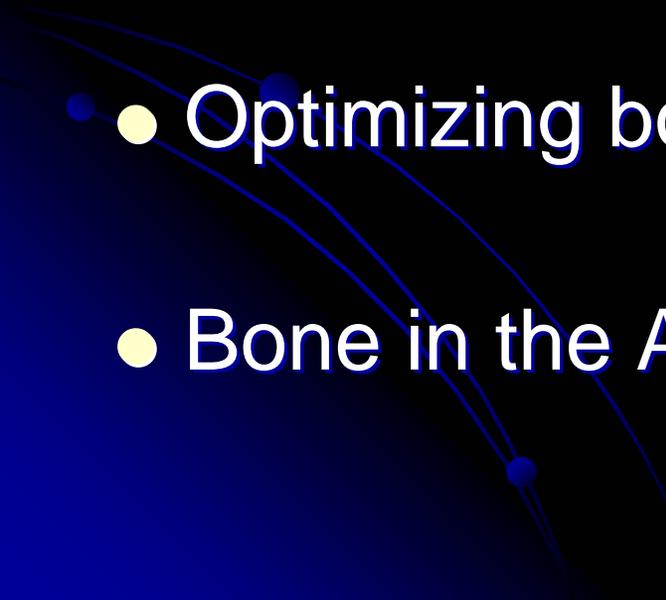
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Presentation Outline

- Fracture risk & Measures of bone strength in RS
 - Contributors to decreased bone strength
 - Optimizing bone strength acquisition
 - Bone in the Aussie-Rett study
- 

Fracture risk in RS

- 1/3 (35%) with RS in Australia had at least 1 fracture
- Estimated 40% would sustain a fracture by 15 years

Leonard H et al, Dev Med Child Neurol 1999 41:323-8

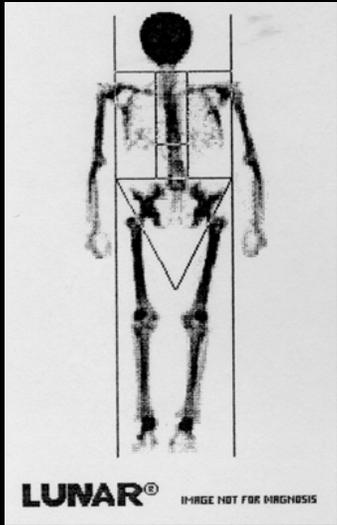
- BUT - Normative Australian data suggests 45% risk of fracture in healthy children <18years

Sherker et al et al, MJA 2004

- Increased risk if
 - risk takers
 - decreased Ca intake
 - immobilization

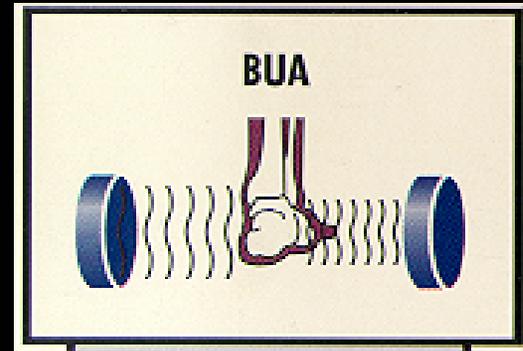
Goulding A et al, J Ped 2005

Bone Mineral

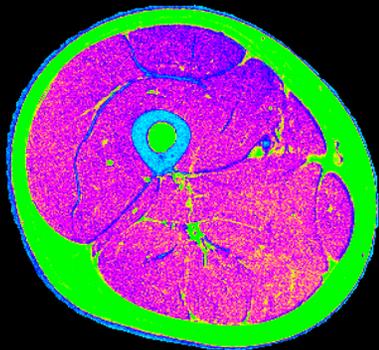


60-80%
Bone Strength

Material Properties



Bone Strength



Bone Geometry



Trabecular Microarchitecture

X-ray studies

Hand and foot X-rays of 94 RS girls + age controls

- Short 4th metatarsal and ulna in > 50% > 5years
- Short 4th metacarpal 2x as common in RS cases as controls
- Earlier maturation vs controls

Geometry via Radiogrammetry of 2nd metacarpal

- 80% had cortical thinning, 1/4 severe
- Mean cortical thickness -1.94SDs RS vs -0.38 controls (p<0.001)
- Cortical thinning
 - Related to anticonvulsant use
 - Not related to calcium intake

Densitometry & Material properties

- 82 girls (2-21y) versus age controls
- DXA (radius), US (calcaneus, phalanges)
- Didn't adjust for size
- RS girls
 - Decreased aBMD proximal and distal radius
 - Decreased SOS, BUA and stiffness at calcaneus
 - Ambulatory significantly greater DXA & US values
 - Anticonvulsants = lower values
 - 25 OH vitamin D levels < controls

Bone strength in RS - biopsy

- Bone histo-morphometry (iliac crest biopsy after tetracycline double labelling)
- 5 girls (9-14 years), at scoliosis surgery
 - Decreased bone volume
 - Normal or **decreased formation** (osteoid surface)
 - Decreased resorption (osteoclast surface & no.)

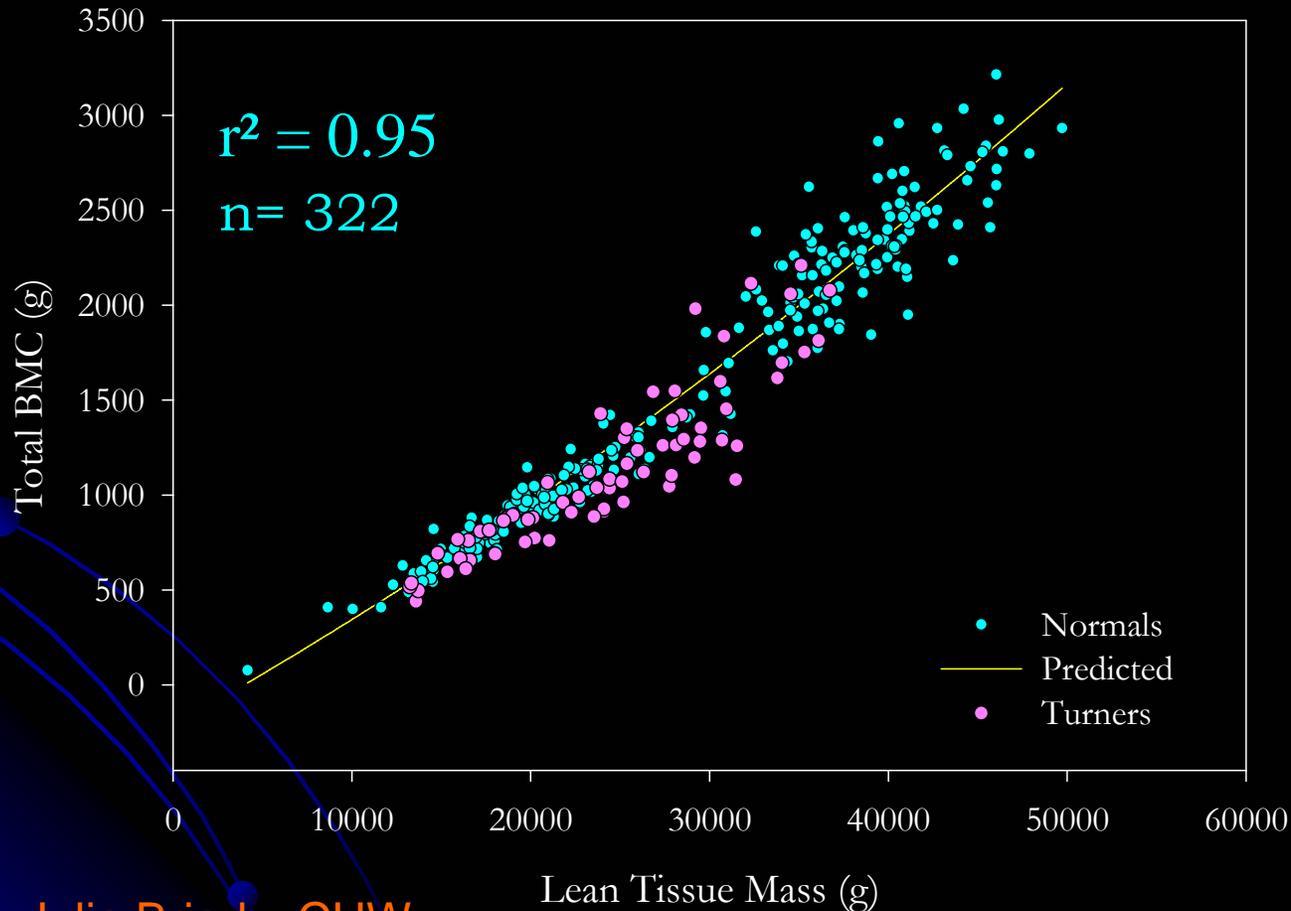
Contributors to decreased bone strength in RS

- Muscle strength
- Calcium intake
- Vitamin D
- Delayed puberty/ suppression of menstruation

With an increased propensity to fall

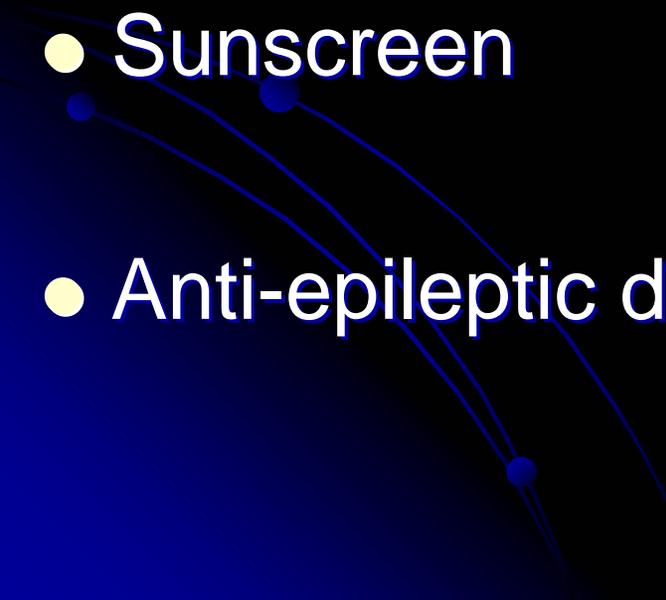
Muscle strength and bone

The muscle bone unit



Courtesy Julie Briody, CHW

Vitamin D deficiency

- Diet (fatty fish, eggs, liver, fortified margarine)
 - Decreased sun exposure
 - Sunscreen
 - Anti-epileptic drugs
- 

Optimize bone strength acquisition

Address risk factors in everyone

- Muscle strength
 - Maximize weight-bearing activity
 - If can't, physio / hydrotherapy
- Calcium intake
 - Meet RDI
 - If can't, calcium supplements (1200mg/ day)
- In delayed puberty, consider sex hormone therapy
- For menstrual suppression, consider OCP rather than provera

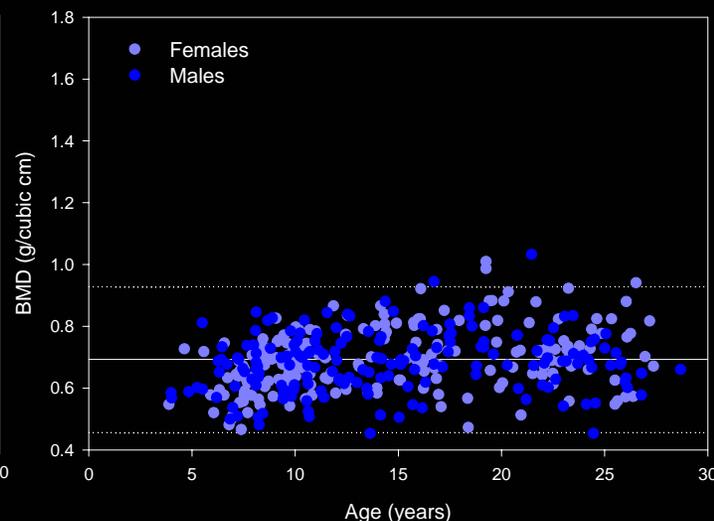
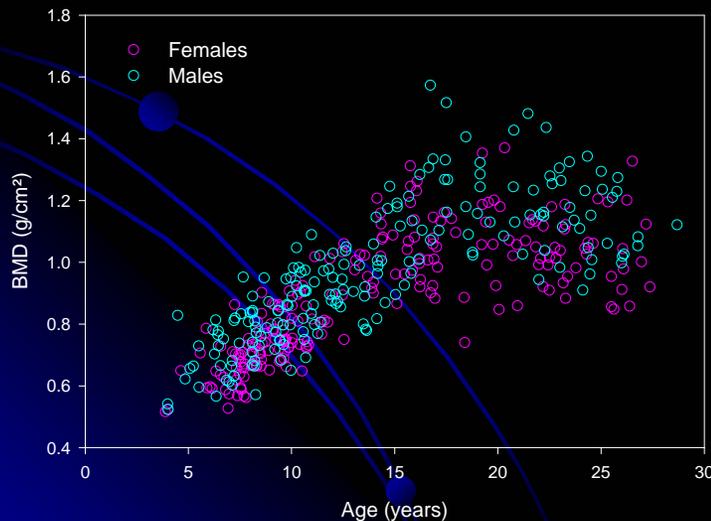
Optimize bone strength acquisition

Vitamin D

- Adequate sun exposure without sunscreen, daily
 - Face, hands and arms for 6-8minutes (summer), 30mins (winter)
Henderson et al 1997 J Child Neurol 12:443-7
- Diet rich in vitamin D
- Consider supplements if inadequate/ high risk
 - 400-800IU daily
- Screening in high risk (anti-epileptics, dark skin, covered, malabsorption)
 - 25 hydroxy vitamin D, calcium, phosphate, alkaline phosphatase, PTH
- Treatment, then supplements, in deficient
 - 3000-5000IU daily for 3+months, with monitoring

Assess bone strength in girls with pathological/recurrent fracture or bone pain

- Densitometry (DXA scan)
 - Dependent on weight/ height/ puberty
 - Needs expert scanning & interpretation



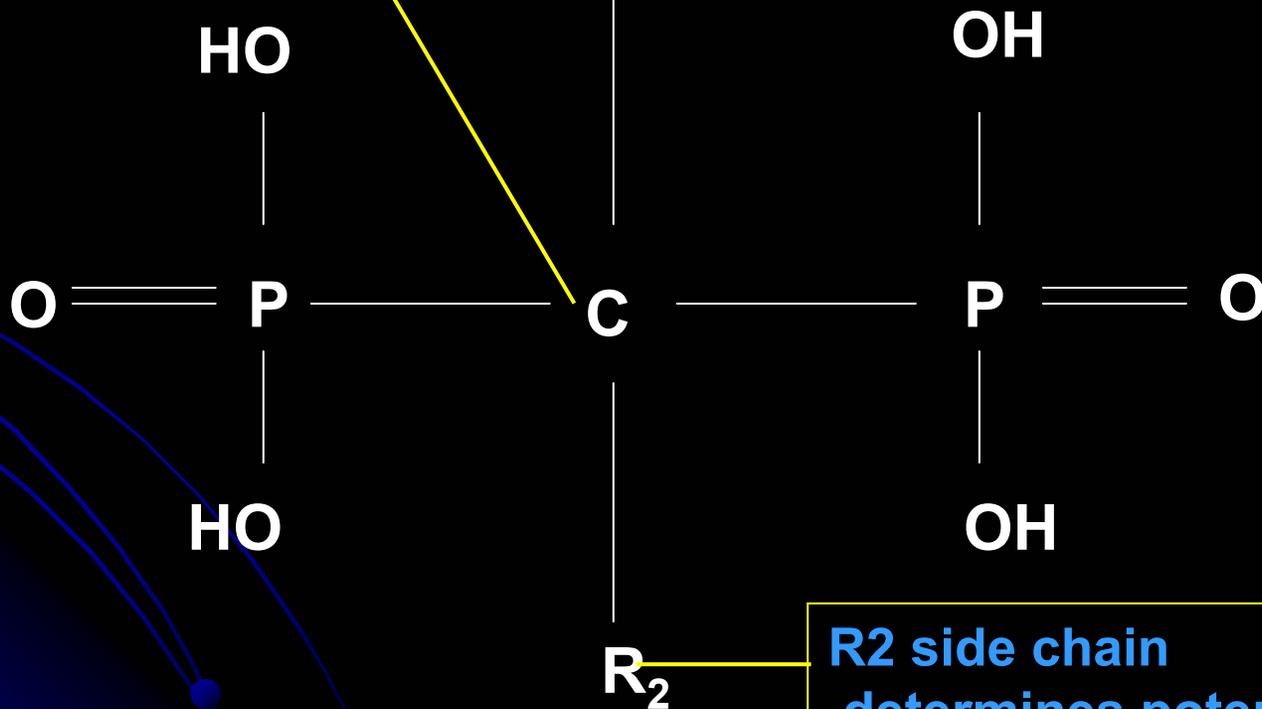
Courtesy Julie Briody, CHW

Bisphosphonates: structure

P-C-P group is
Essential for

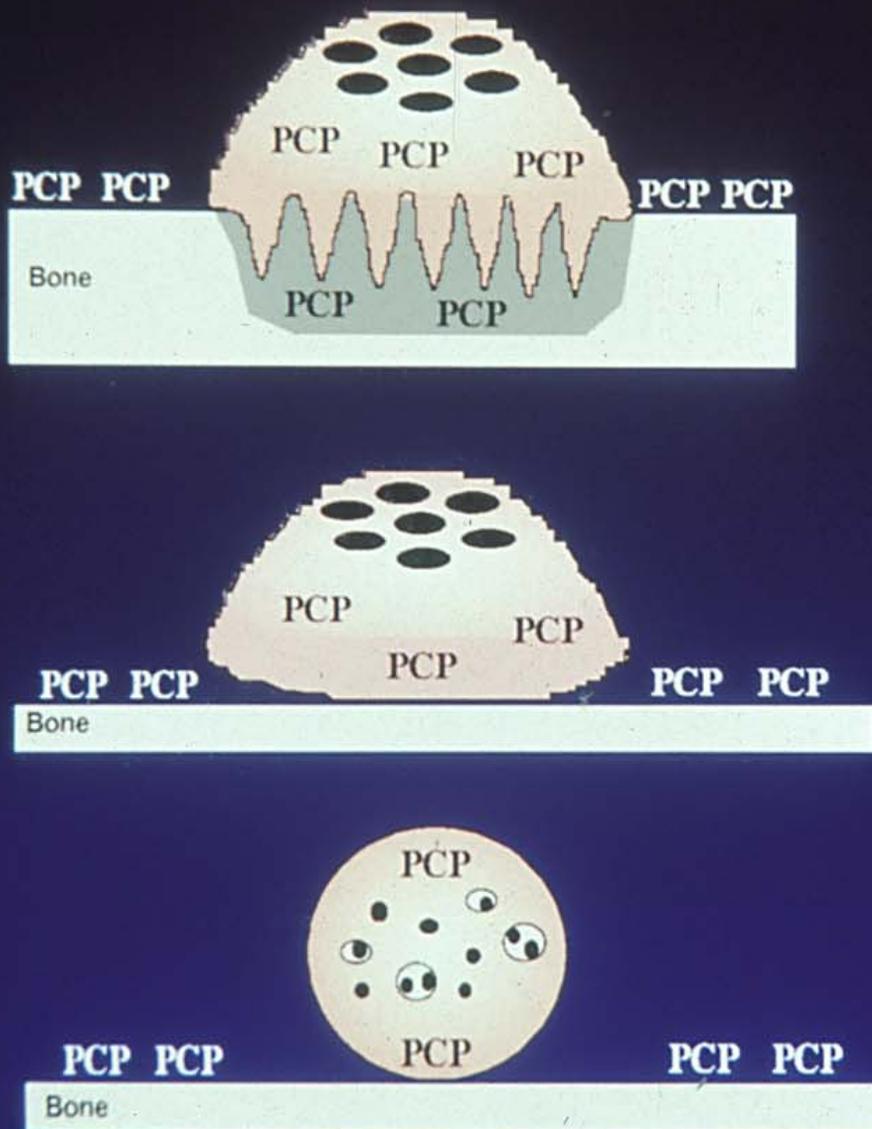
- Binding to hydroxyapatite
- Biological activity

When R₁ is an OH,
binding to
hydroxyapatite
is enhanced



R₂ side chain
determines potency

Bisphosphonates: action



**intracellular uptake of
bisphosphonate by osteoclasts
during resorption**



loss of resorptive function



apoptosis

Formation > ↓ Resorption = net ↑

Bisphosphonates: sequelae

Mainly with IVI, not oral therapy- from studies in OI

- “flu-like” illness in 83%
 - Fever, joint and bone pain, vomiting
 - Mainly with 1st dose
 - Relieved by use of brufen
- Transiently low calcium
 - Worse if low calcium / vitamin D deficient
- Uveitis
- ? Nephrocalcinosis
- ? Teratogenic risk – long half life, crosses placenta

? Bisphosphonate therapy

- Needs careful investigation, consideration then management by endocrinologist/ bone physician
- Only with fracture/ bone pain
- No outcome study results in RS
- Better results with
 - IVI vs oral
 - Pre- and pubertal children, rather than post-pubertal
 - High bone turnover states
- If considered, should be done in a study trial

Aussie-Rett study

- Multi-centre, across Australia
- All RS children and young adults, 2005 & 2007
- Fracture history
 - number/ site(s)/ age/ mechanism of injury
- Bone mass and geometry (DXA)
- Contributing variables
 - Genotype
 - Family history of osteoporosis (questionnaire)
 - Medical history and medications (questionnaire)
 - Muscle strength (mobility assessed by video)
 - Muscle size (DXA)
 - Ca intake (food frequency questionnaire)
 - Vitamin D (Sun exposure and sunscreen use-questionnaire)
 - Height/ Weight and pubertal status (Tanner stage)
 - Vitamin D status (bloods) and turnover if low DXA, in 2007