Osteoporosis/ Osteopenia in RDEB- what's new?

4th Conference EB-CLINET

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Outline

- Review of the literature
- Bone basics
- Risk factors for osteopenia in EB
- What's new
  - Retrospective study of children with RDEB at GOSH
  - Current status of bone health
- What's next

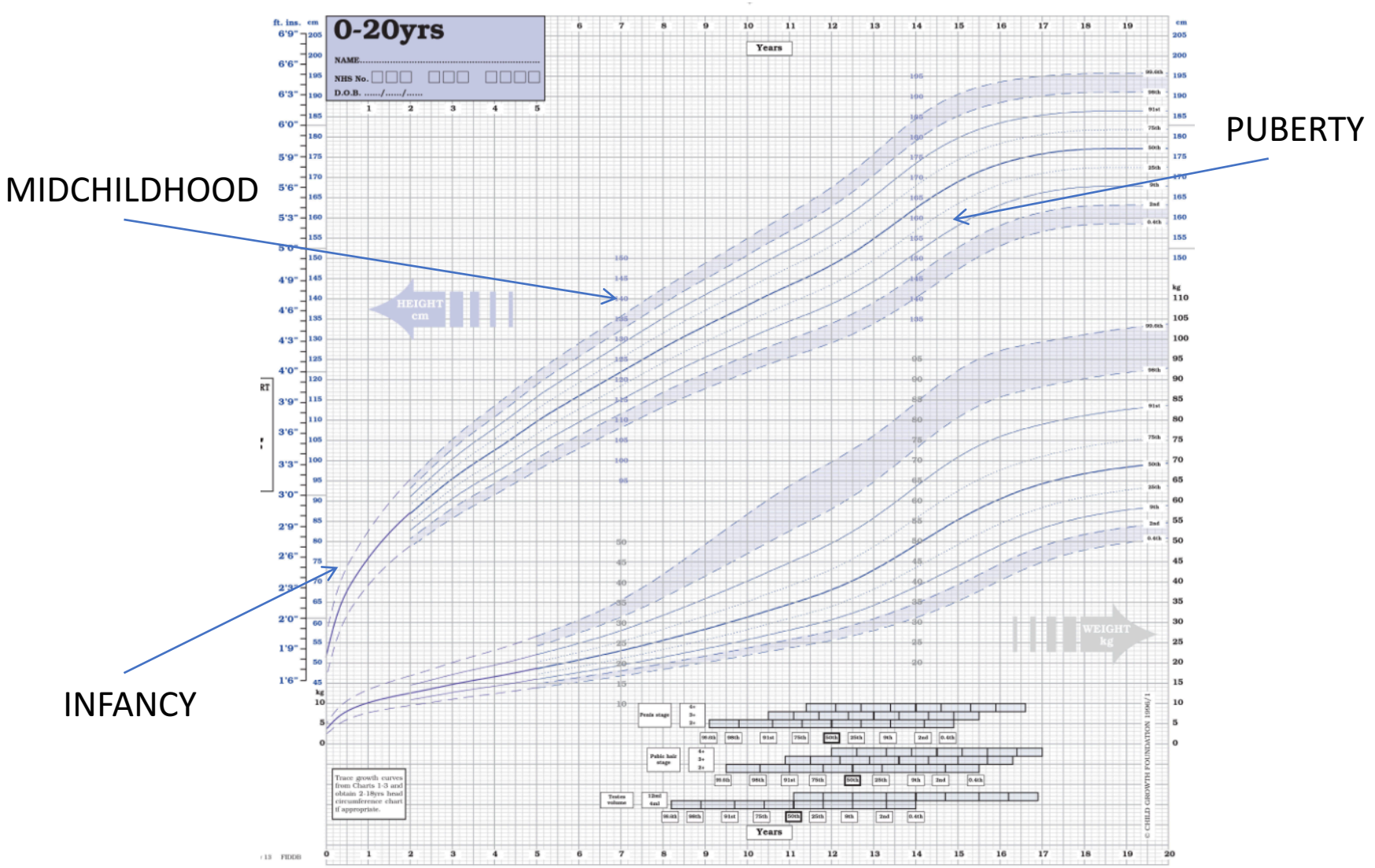
Current key literature bone health

- Francis Palisson group 2002
  - 7 children generalised EB
  - 3 had reduced BMD, low Vit D and severe limited mobility
- Anna Martinez group 2006
  - 39 children
  - All RDEB and JEB low BMD compared to matched controls
  - Correlation with inactivity not with Vit D

Current key literature bone health

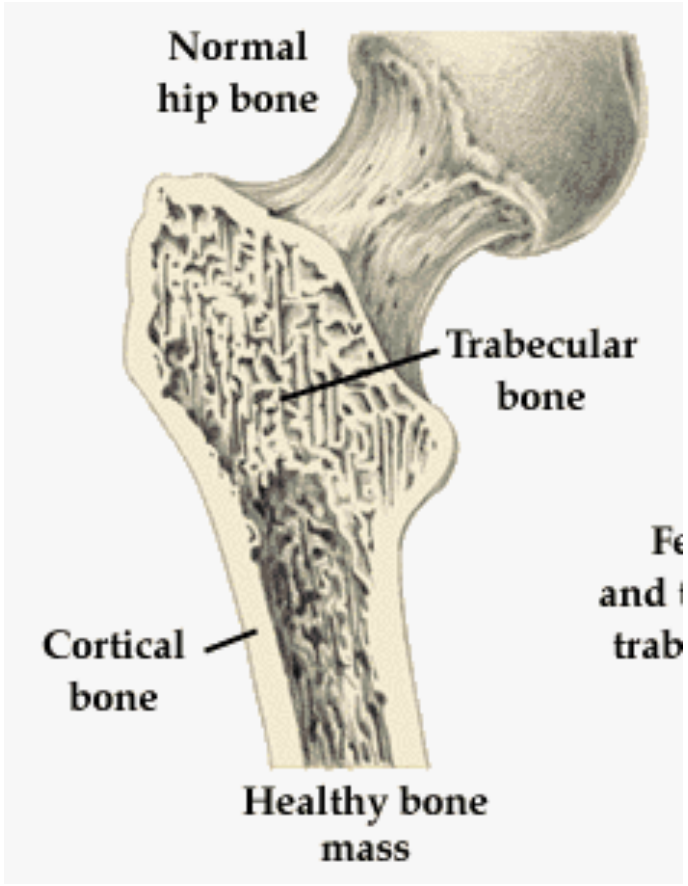
- Anna Bruckner group 2011.
  - prospective study 24 children 2 centres
  - 20 RDEB had low aBMD
  - mobility was associated with low aBMD but not Vit D levels
- Tivoli in Milan 2017.
  - 20 children all 4 types of EB (10 RDEB)
  - Reported an association with Birmingham EB severity score & Vit D status with low BMD

3 chances to get our bone banked

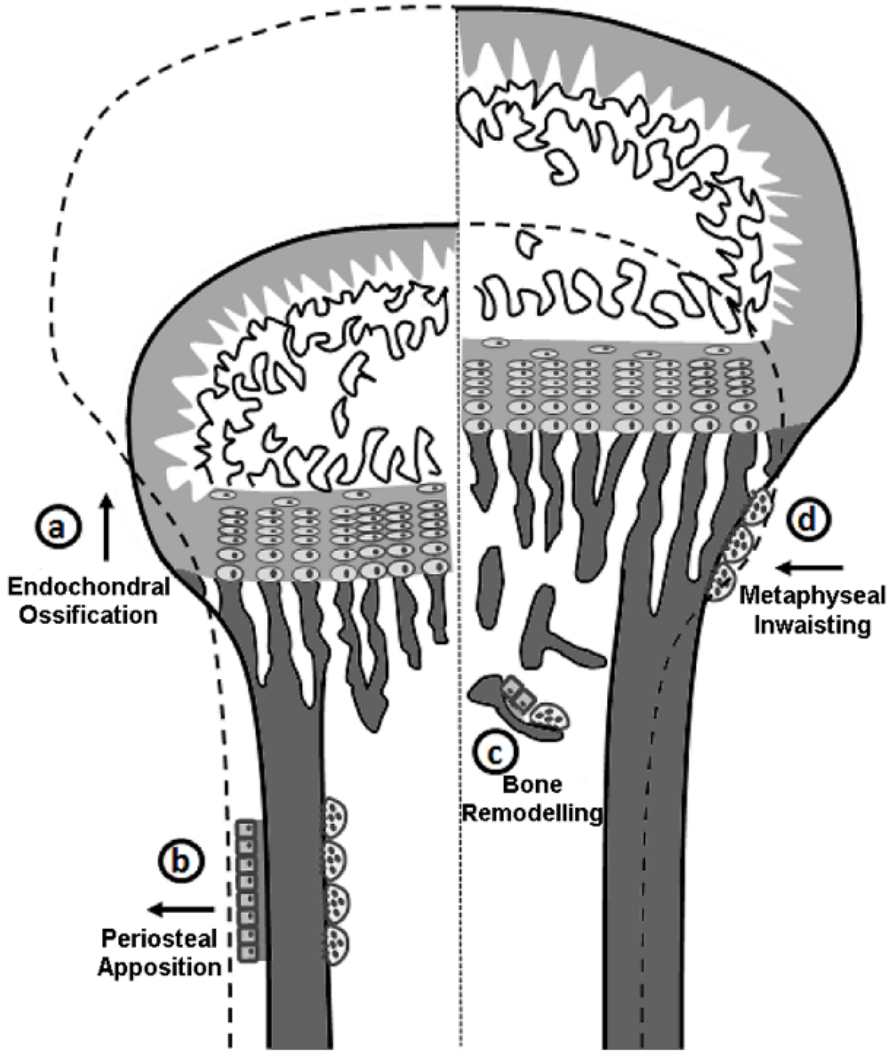


Two Types of bone

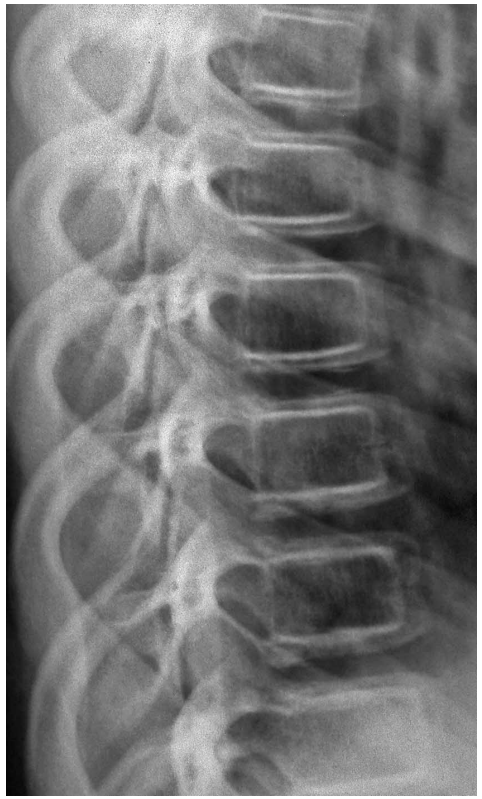
- Cortical
  - dense outer part 80% weight of bone
- Trabecular bone
  - end of long bones
  - inside vertebral bodies
    - metabolically active bone

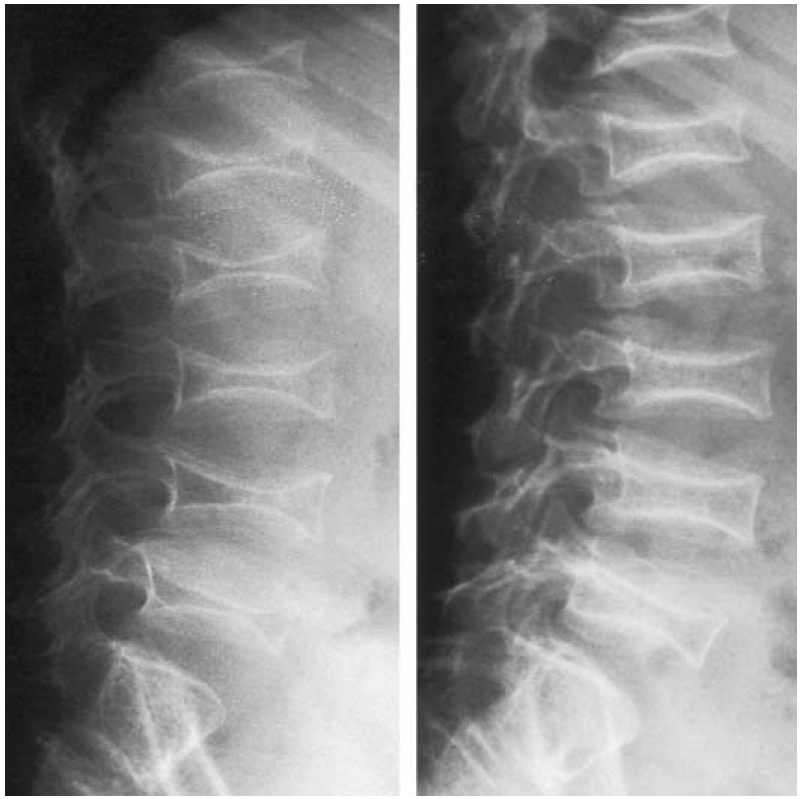


Long Bones

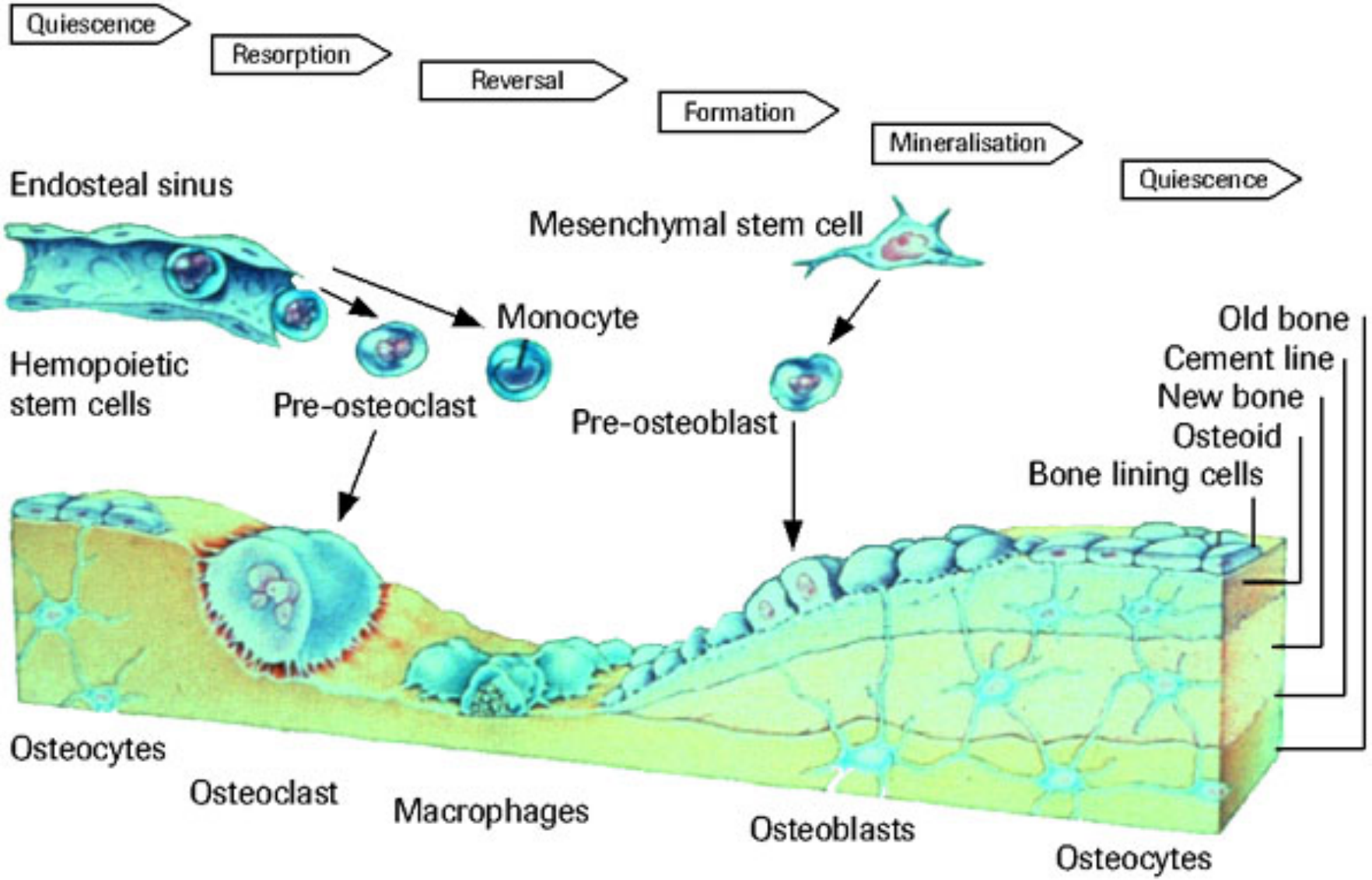

a
Endochondral Ossification
b
Periosteal Apposition
c
Bone Remodelling
d
Metaphyseal Inwaisting

Vertebral Bodies



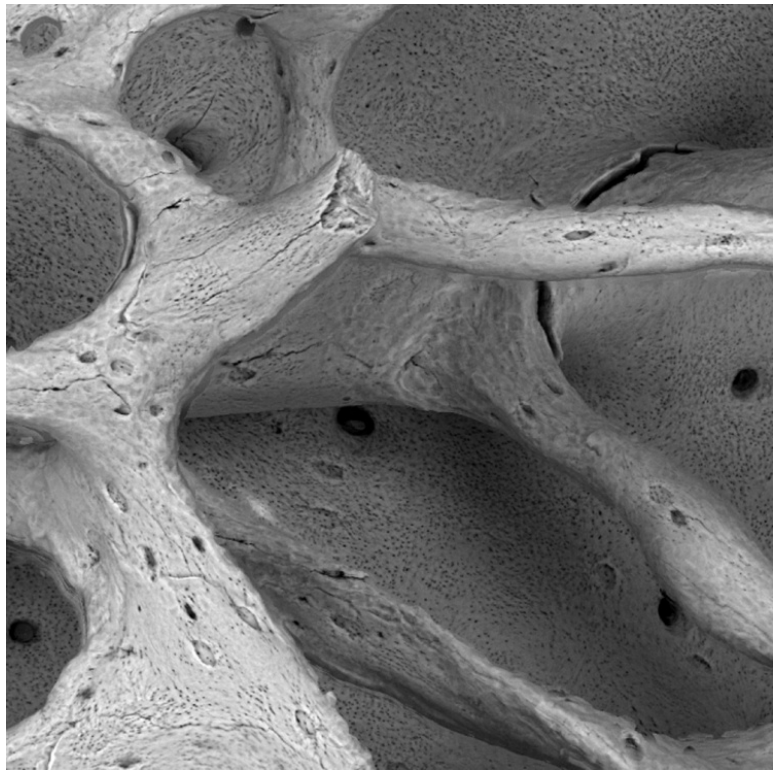


Bone remodelling cycle



Osteocytes

- Osteocytes make of 90% of the body's bone cells in connecting network
- This networks feed back mechanical strain to the osteoblasts & osteoclasts

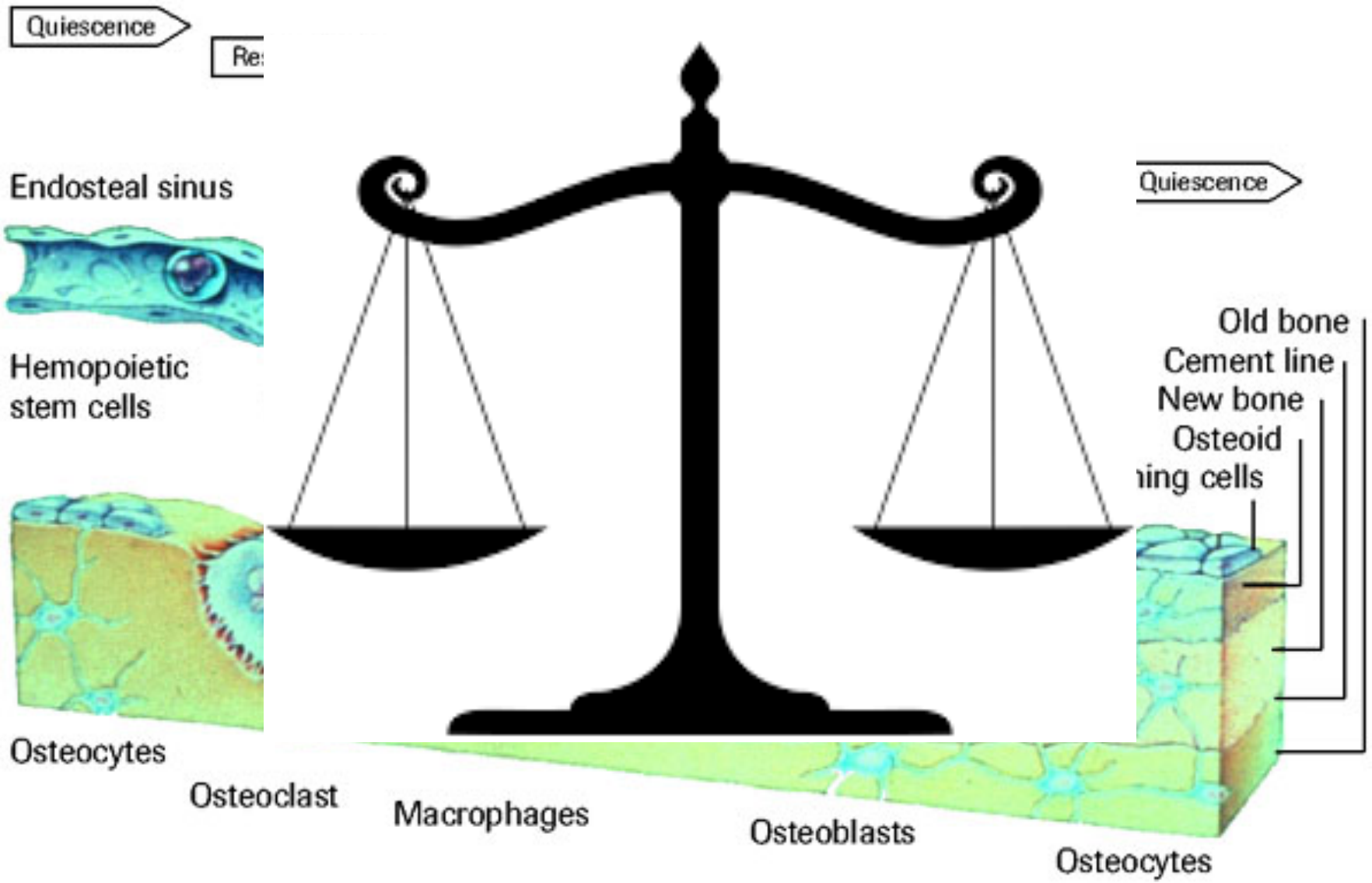


Osteocytes

- Produce 2 essential cytokines
  - nuclear factor kappa B (NF-kB) ligand (RANKL)
  - macrophage colony-stimulating factor (M-CSF)

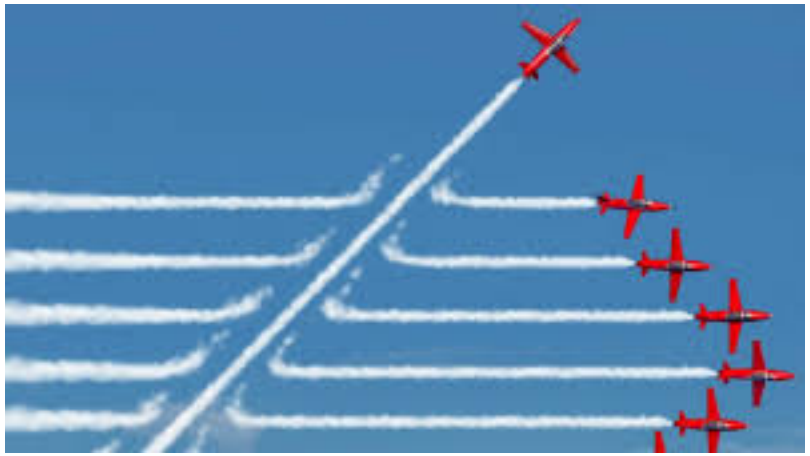
- Cytokines critical regulation osteoclast activity

Bone remodelling cycle



Bone strength dependent is on

- Mobility- bone loading
- Good nutrition- calcium and vit D
- Attainment of puberty
- Healthy and adequate numbers of bone cells

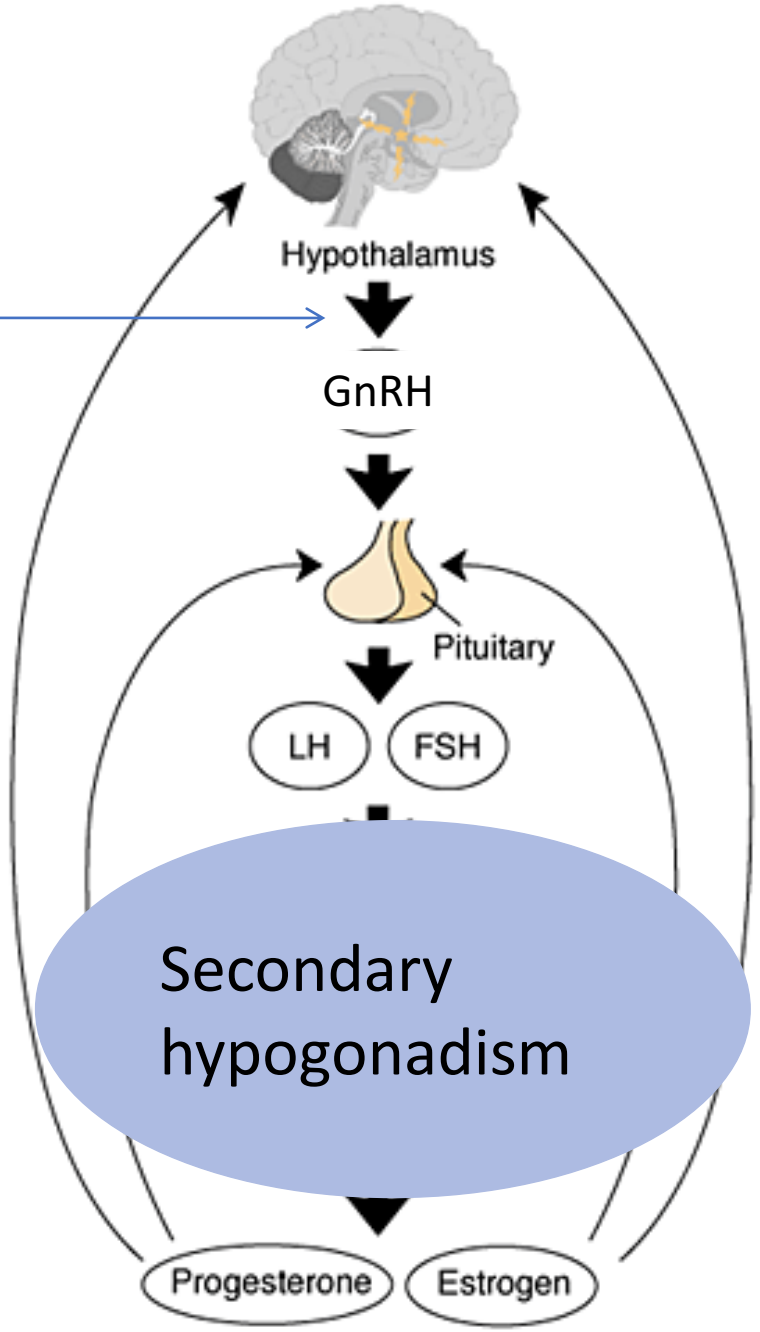


Pubertal delay in EB patients

- Central delay as in other chronic inflammatory diseases

- Reduction GnRH
  - reduction FSH/LH

IL-6


Hypothalamus
GnRH
Pituitary
LH
FSH
Secondary hypogonadism
Progesterone
Estrogen

Puberty in EB patients

- Skeletal mass approximately doubles during puberty

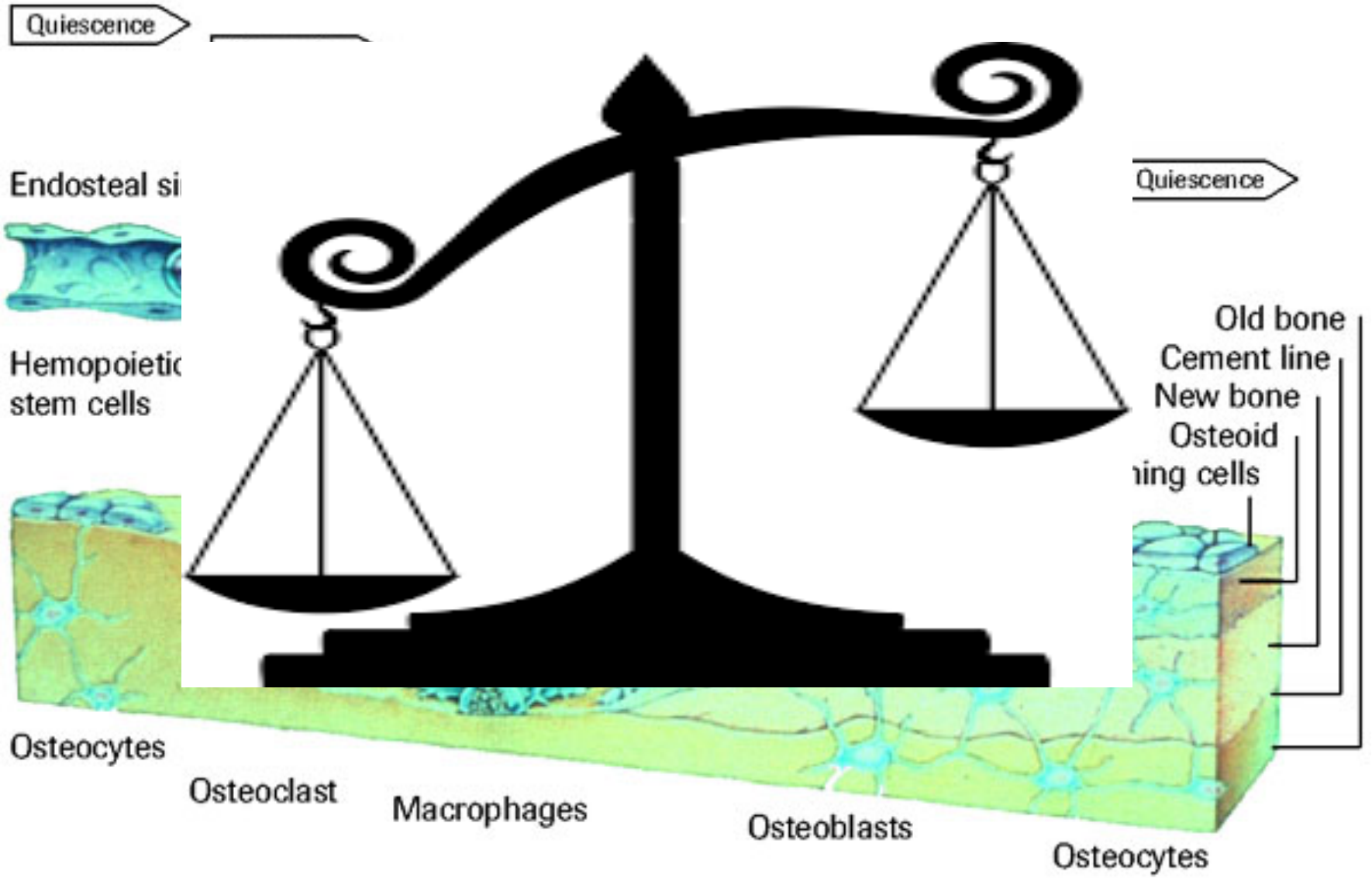
Abnormal bone regulation

- Inflammation
  - activation of inflammatory cytokines
    - interleukins 1 & 6
    - TNFα
    - RANKL

Abnormal bone regulation

- Reduction mesenchymal stromal cells
  - Dr Tamai mentioned on Monday
  - Osteoblasts originate from these cells
  - This is likely to have impact on bone building potential in patients with EB

Bone remodelling cycle



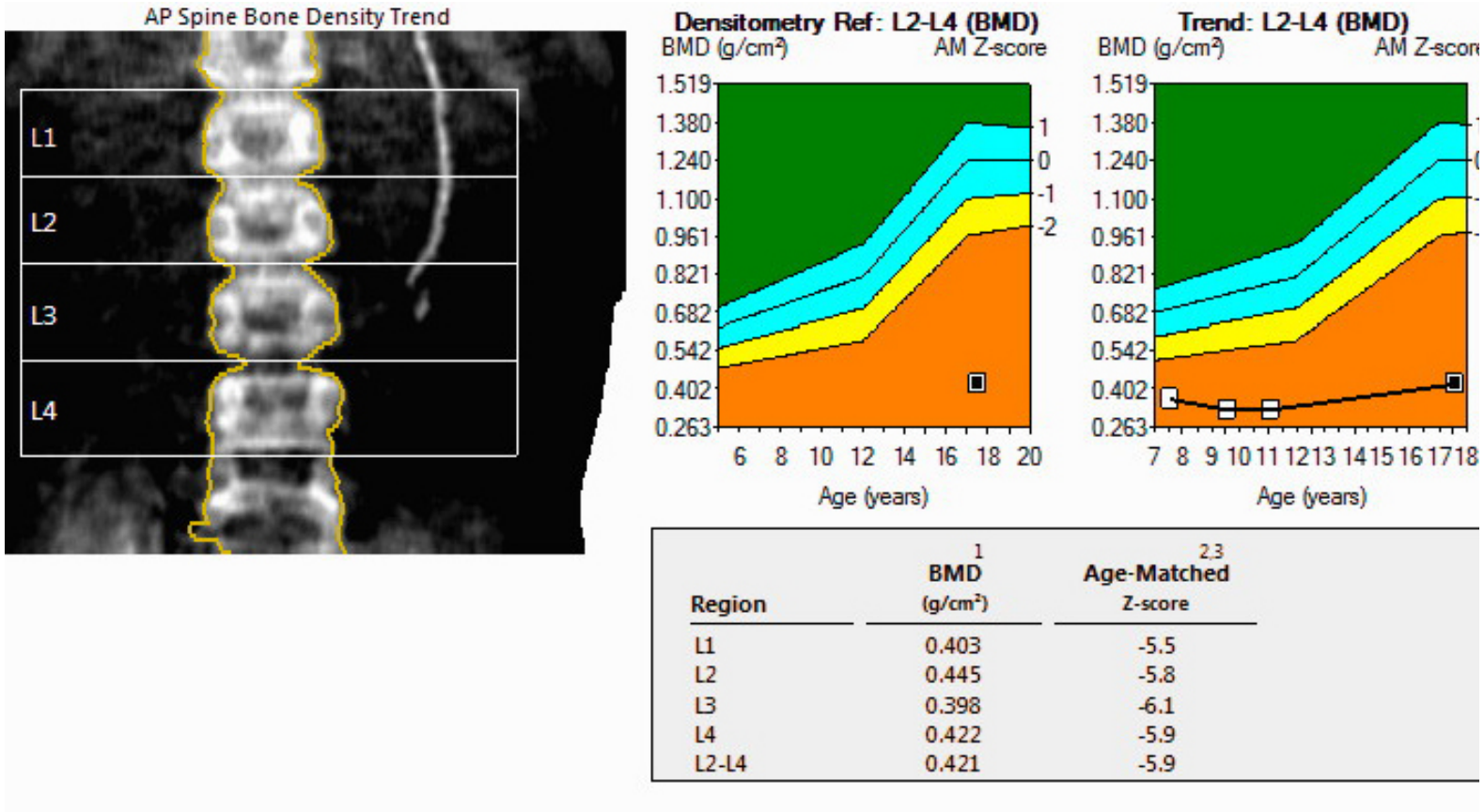
Retrospective comparison of bone health in children with RDEB

- Jan 2000-Aug 2007
- 40 patients with RDEB aged 7-8 and 15-18 years
- 20 in each group

Primary outcome measures

- vertebral fractures
- scoliosis
- pubertal delay
- lumbar spine aerial Bone Mineral Density (aBMD)
- age adjusted Z score (Z-score)

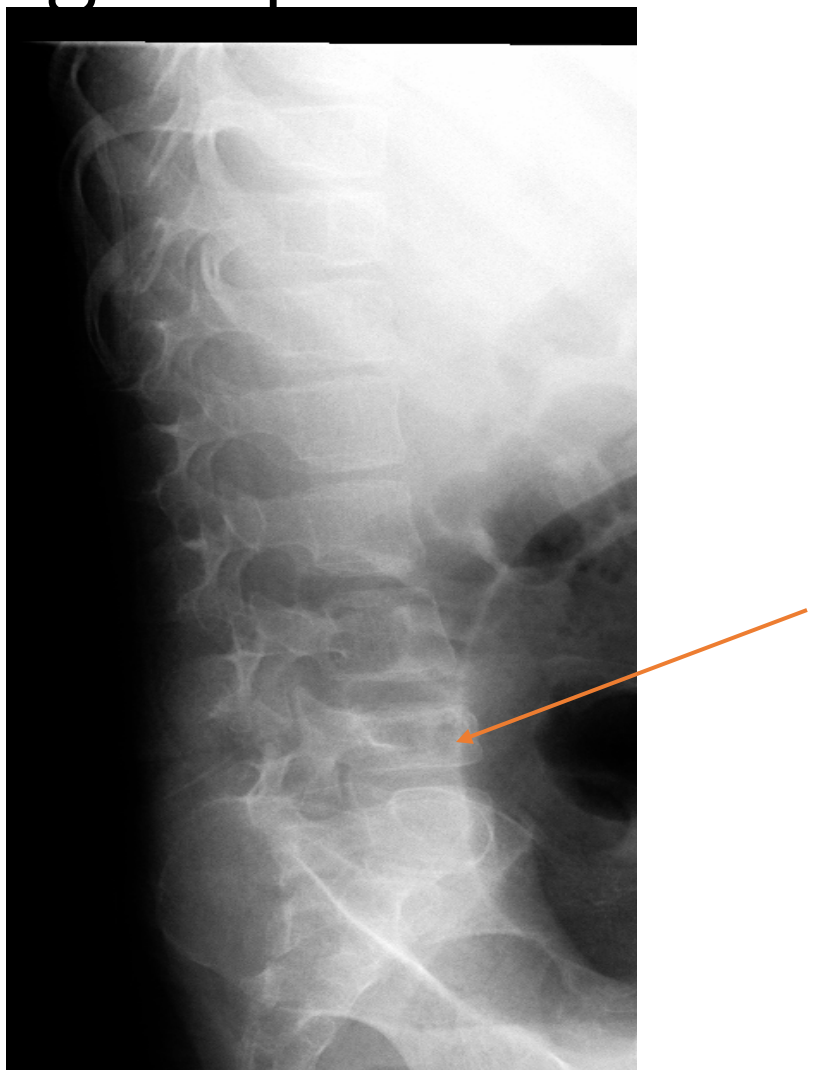
Lumbar areal Bone Mineral Density



Region	BMD[1] (g/cm²)	Age-Matched[2,3] Z-score
L1	0.403	-5.5
L2	0.445	-5.8
L3	0.398	-6.1
L4	0.422	-5.9
L2-L4	0.421	-5.9

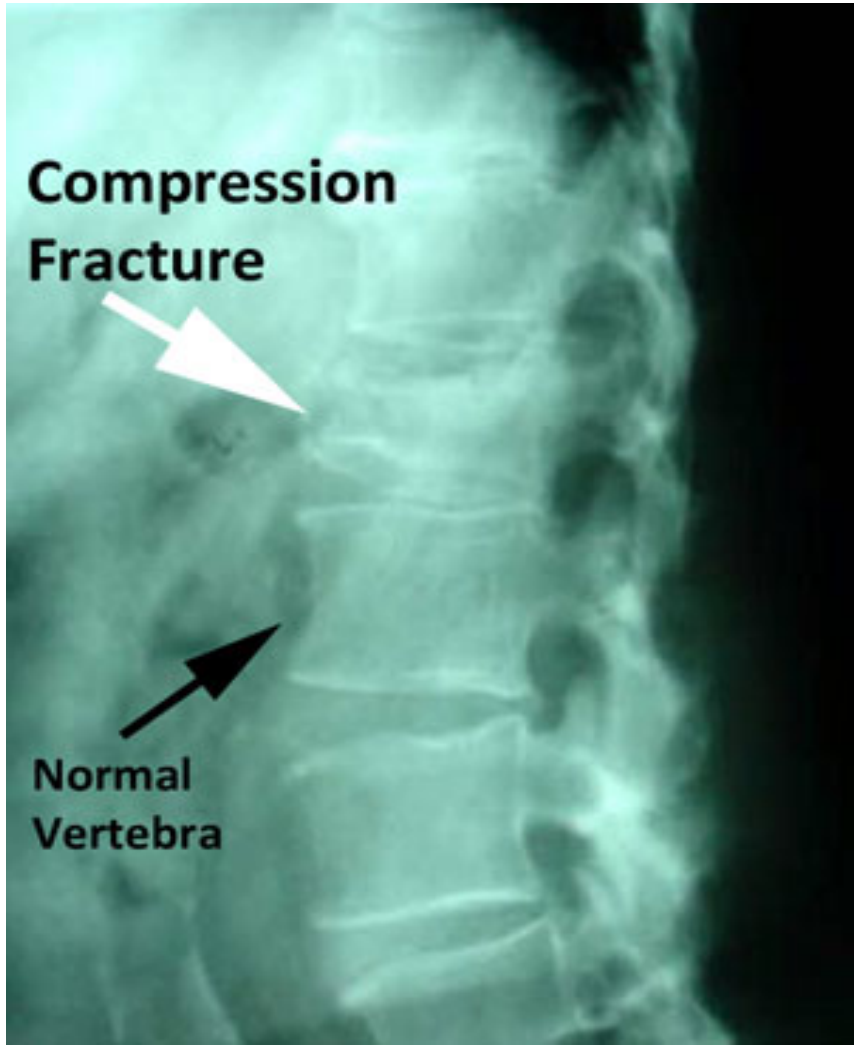
Results 7-8 year old RDEB group 2007

- 36% had vertebral fractures
- 11% had scoliosis



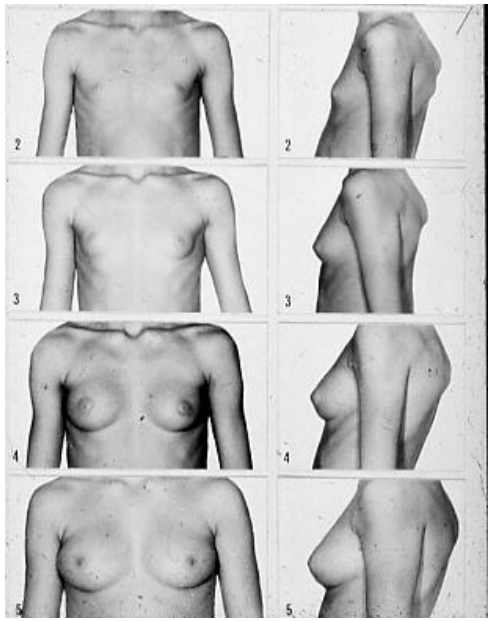
Results 15-16 yr old RDEB group 2007

- 40% had vertebral fractures
- 30% had scoliosis
- 84% of these children had pubertal delay.



Pubertal delay definition

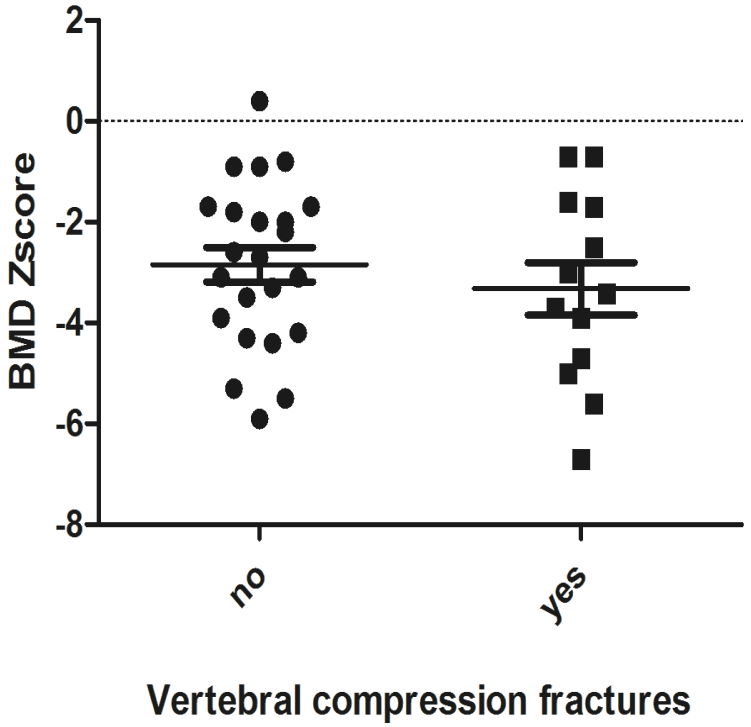
- Girls:
  - no breast development by 13 years in girl
  - no Menarche by 16 years
- Boys
  - testicular volume <4mls before 14 years



Results

- There was a highly significant decrease in BMD Z score ($p<0.0001$) with age

Abnormal BMD scores are not a fracture predictor



- Surprisingly patients with fractures did not have significantly different BMD Z-scores from those without (P=ns, t-test).

Results

- Fractures present silently in vast majority cases
- Youngest child female age 5.75 years

Results in 2017 age 7-8 yrs.

- 6 children
  - 1 fracture

Age 8 girl

- 8 year old girl
- Fully mobile
- Normal biochemistry
- Presented July 2017 sudden onset back pain whilst in shower
- Last screen X-rays April 2017 normal

Age 8 girl

- Loss of 25% vertebral body height L2-L5
- Depression endplates
- Boxes collapsed

Results 15-16 yr old RDEB group 2017

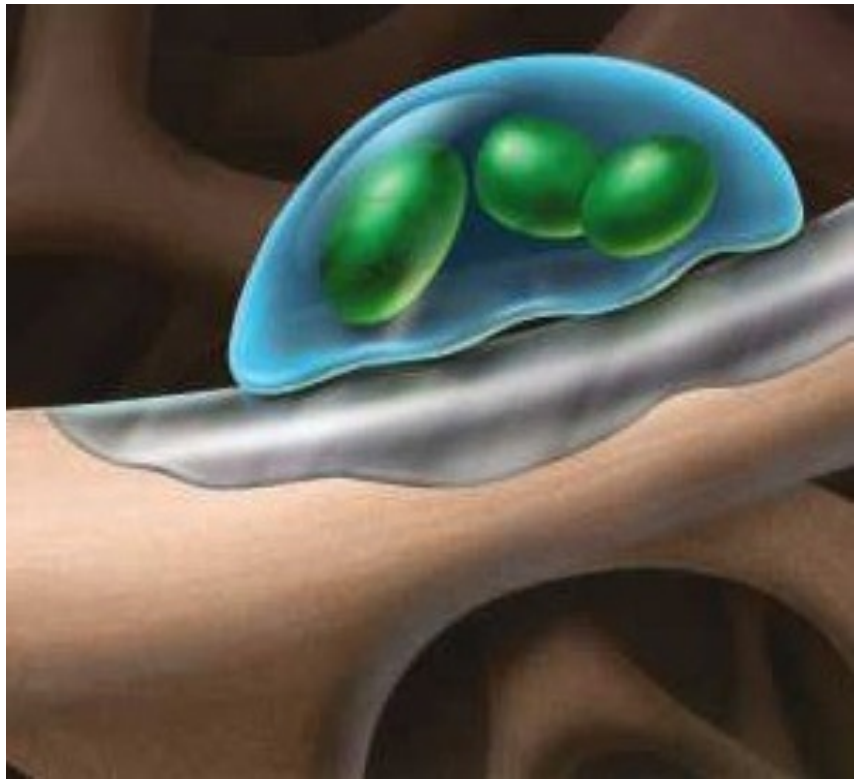
- 3 children
  - no fractures
  - all reached puberty

Proposed screening & monitoring of bone health in RDEB

- Lateral spine X-ray annually from age 5 years
- DEXA
  - baseline age around puberty
  - before starting bisphosphonates
  - annually for monitoring treatment

Treatment of fractures

- Use bisphosphonates well tolerated
- Intravenous zoledronic acid
  - short infusion
  - 6 monthly
  - highly effective OI



We are making a difference

- In many ways
- Better overall care

How can we prevent fractures?

How can we prevent fractures?

- Optimize
  - nutrition
  - wound care
  - mobility

Pubertal attainment crucial

- Endocrinologist
- Psychologist

The future

- Good longitudinal studies of bone health
- Trials of non pharmacological interventions such as vibration platforms
- Pubertal attainment is critical to bank more bone mass and reduce fracture risk
- Consider new medicines for osteoporosis
  - Denosumab anti-RANKL

Acknowledgements

- Dr Moira Cheung
- All patients & team at GOSH