Other bone diseases

Juliet Compston
Professor of Bone Medicine
University of Cambridge School of Clinical Medicine
Clinical outcomes of bone disease

- Pain
- Deformity
- Fracture
Determinants of bone strength

• Bone mineral density

• Bone geometry

• Bone quality
Measurement of bone mineral density

• Reasonable predictor of fracture risk in untreated state

• Less good predictor of fracture risk in treated patients
### Relationship between therapeutically induced BMD increase and vertebral fracture reduction

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>% Fx reduction explained by BMD</th>
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</thead>
<tbody>
<tr>
<td>Cummings</td>
<td>Alendronate</td>
<td>16%</td>
</tr>
<tr>
<td>Sarkar</td>
<td>Raloxifene</td>
<td>4%</td>
</tr>
<tr>
<td>Li</td>
<td>Risedronate</td>
<td>28%</td>
</tr>
</tbody>
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**Individual patient data analysis**

Determinants of bone strength

- Bone mineral density
- Bone geometry
- Bone quality
Bone geometry: size and shape

Mainly determined by genetic factors

• Some aspects e.g. size, cortical thickness can be modified by exercise, diet, anabolic therapy

• Other aspects e.g. femoral neck length are non-modifiable
Effect of PTH peptide 1-34 on cortical width and bone size

Patient 1124

Female, age 65
Duration of therapy: 637 days (approx 21/12)
Baseline BMD:
Spine T-score = -2.0
Femoral neck T-score = -2.6
Response:
Spine +7.4%
Femoral neck +3.5%
Determinants of bone strength

- Bone mineral density
- Bone geometry
- Bone quality
What is bone quality?

- Bone quality refers to material and structural properties of bone.
- Some, but not all of these are captured by measurements of bone mineral density.
- Changes in bone quality may contribute to changes in bone strength in untreated and treated bone disease.
Components of bone quality

- Bone turnover
- Bone microarchitecture
- Mineralisation
- Microdamage
- Matrix and mineral composition
What is bone turnover?

- Remodelling rate: the number of remodelling units
- Remodelling balance: the relative amounts of bone resorbed and formed within individual remodelling units

Bone turnover = remodelling rate x focal balance

(from Mosekilde Bone Miner 1990;10:13-35)
Bone microarchitecture

- Cancellous bone
  - connectivity
  - anisotropy
  - trabecular shape and size

- Cortical bone
  - cortical thickness
  - cortical porosity

Dufresne, et al, 2004
Degree of mineralisation of bone

The degree of mineralisation of bone is inversely related to bone turnover.

Primary mineralisation: mineralisation during bone remodelling cycle

Secondary mineralisation: subsequent slow and gradual maturation of mineral and increase in its amount
Changes in collagen maturation with age

14-yr old  72-yr old
Fourier Transform Infra-Red (FTIR) spectroscopy: mineral crystallinity

Normal

OP

OP + F

Courtesy of EP Paschalis
Detection of microdamage in iliac crest biopsies
Relationship between bone turnover and bone strength
(from Weinstein, JBMR 2000)

Bone turnover

- Hypermineralisation
- Impaired microdamage repair
- Reduced osteocyte viability

Bone strength

- Hypomineralisation
- Reduced bone mass
- Stress risers
High turnover states associated with increased fracture risk

- Postmenopausal osteoporosis
- Post-transplantation osteoporosis
- Immobilisation osteoporosis
- Secondary hyperparathyroidism
- Paget’s disease
Adynamic renal bone disease

- Characterised histologically by very low bone formation rates and presence of very little osteoid
- Associated with low or low-normal serum PTH levels
- Fracture risk not well documented but some evidence for higher prevalence of vertebral and hip fractures in patients with ESRD and low PTH levels
Effect of bisphosphonates on microdamage in dogs

Mashiba et al 2000, 2001
Komatsubara et al 2004
“Severely suppressed bone turnover” in patients treated with alendronate: ? a causal association

- 9 patients receiving alendronate for 3-8 yrs
- 3 also receiving HRT, 2 prednisolone
- Presented with spontaneous non-spinal fractures ± non-healing of fractures
- Bone biopsies all showed absence of double tetracycline labeling, cells virtually absent from bone surfaces
- Only 2 had osteoporosis (T-score $\leq -2.5$)

(Odvina et al, JCEM 2005;90:1294-1301)
Atypical femoral fractures in patients on long-term alendronate

Usually simple transverse or oblique
Cortical thickening on lateral aspect, medial beaking of cortex
Prodromal pain common
May be bilateral
Exhibit poor healing
Atypical femoral stress fractures
Hypomineralisation of bone is associated with increased bone fragility: osteomalacia

- Characterised by reduced mineralisation of bone
- Associated with pseudofractures and pathological fractures
Hypermineralisation of bone is associated with increased bone fragility: osteopetrosis

- Diverse phenotypes and genotypes
- Associated with increased bone mass and increased degree of mineralisation of bone
- Osteopetrotic bone is stiff and brittle
- Often associated with fractures
Sclerosteosis and Van Buchem disease

- Associated with absence/reduced production of sclerostin
- Autosomal recessive disorders
- Characterised by endosteal hyperostosis
- Resistance to fracture
- Excessive height and syndactyly (sclerosteosis)

Courtesy of Wim van Hul
Paget’s disease of bone
Osteogenesis imperfecta

- Defective synthesis of type 1 collagen

- Associated with
  - abnormal matrix/mineral composition
  - abnormal mineralisation density of bone
  - abnormalities of bone modelling and architecture
  - increased risk of fracture
SS vs ss genotype:

- SMD spine BMD 0.20 (0.07-0.34) Z score units; p=0.004

- OR fracture 1.86 (1.26-2.70); p=0.001

(from Mann et al, JCI 2001;107:899-907)
Osteoclastic bone resorption

Proteases e.g. cathepsin K, MMPs

H+ ATPase + chloride channel

Ruffled border

Sealing zone

Mineralised bone

Clear zone

Dissolution of bone mineral and matrix
Cathepsin K deficiency: pycnodysostosis
Fibrous dysplasia

- Monostotic and polyostotic forms

- Extraskeletal manifestations include hyperpigmentation of skin, endocrine dysfunction and renal PO4 wasting

- Caused by activating mutations of the GNAS gene (encoding the $\alpha$ subunit of $G_s\alpha$)
Fibrodysplasia ossificans progressiva

- Progressive, disabling heterotopic osteogenesis, chondrogenesis and joint fusions

- Caused by an activating mutation of ACVR1, a BMP type 1 receptor (Shore et al, Nature Genetics, 2006)
Glucocorticoids increase fracture risk independently of BMD

(from Kanis et al 2004)
Direct effects of glucocorticoids on bone

Increased bone resorption (early, transient)

- RANKL
- M-CSF
- Formation
- Apoptosis

Decreased bone formation (long-term)

- PPARγ
- Wnt signalling
- Activation of caspase 3
- Proliferation
- Apoptosis

Apoptosis
Time course of vertebral fractures during glucocorticoid use
(from van Staa et al, JBMR 2000)
Assessment of bone quality in clinical practice

- **In vivo**
  - Clinical signs
  - X-rays
  - Bone biochemistry
  - pQCT

- **Bone biopsies**
  - Turnover
    - Histomorphometry
  - Architecture
    - \( \mu \)CT, histomorphometry, MRI
  - Mineralisation
    - QBSE, microradiography
  - Mineral crystal structure
    - FTIR, EM, SAXS
  - Matrix composition
    - FTIR
Clinical assessment of bone quality: future priorities

• Regional measures of bone turnover

• In vivo assessment of microarchitecture

• Biochemical measures of bone matrix composition