High bone mass and osteoarthritis: an epidemiological observation revisited

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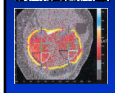
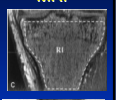
Local and systemic bone changes in knee and hip OA

CT



MRI

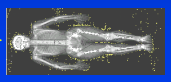


DXA

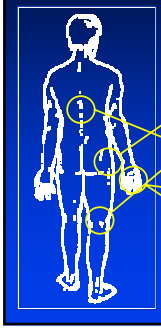
- CT, MRI, DXA to study local/periarticular bone changes in established human OA
  - Changes in bone volume and microarchitecture, bone mass distribution, mechanical properties
- Original epidemiological observation: OA is associated with a high systemic bone density phenotype (arealBMD)
  - 'Systemic' = aBMD at a site distant from joint with OA

DXA

Knee OA



Epidemiological evidence for increased systemic BMD in persons with prevalent OA



Site of OA	Percent increases in BMD: hip	spine	radius	total body
Hip	**5-10**	8	5	?
Knee	2-10	4-7	0	7
Spine	2-6	**7-8**	6	8
Hand	2-3	5	0	?
Generalized	5	10	?	?

OA associated with higher BMD in 43/ 53 studies reviewed (Dequeker, 2003)

Does high systemic BMD precede the development of OA?

- Existing OA can alter BMD locally and at distant sites
  - Local bone hypertrophy /calcification 2° to OA
  - Bone loss due to inactivity /disability
- Prospective cohort study: measure BMD at distant sites before OA develops
  - **Caveat**: Subjects without OA at study joint may have OA at other sites that affects BMD

3 large prospective cohort studies of BMD and Incident x-ray knee OA

Study	Subjects	Follow-up	Incident OA case (n)	X-ray protocol
Framingham (Zhang, 2000)	473 women	8 yrs	KL ≥ 2 (67) OST (140)	Extended AP knee
Chingford (Hart, 2002)	715 women	4 yrs	OST (81) JSN (95)	Extended AP knee
Rotterdam (Bergink, 2005)	619 women 496 men	6.5 yrs	KL ≥ 2 (74) OST (119) JSN (84)	Extended AP knee

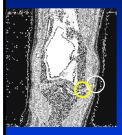
Results of 3 studies BMD and Incident knee OA

Study	KL ≥ 2	OSTeophytes	JSN
Framingham (Zhang, 2000)	↑ RR with: ↑ hip BMD*	↑ RR with: ↑ hip BMD	Too few cases
Chingford (Hart, 2002)	NA	Cases: ↑ hip* BMD ↑ spine* BMD	No assoc
Rotterdam (Bergink, 2005)	↑ RR with: ↑ hip BMD* ↑ spine BMD*	Cases: ↑ hip* BMD ↑ spine* BMD	No assoc

* P< .05

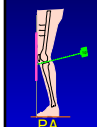
All analyses controlled for age, BMI, gender and other covariates

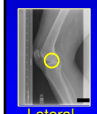
Is systemic BMD only associated with osteophytes?



- Higher BMD predicted onset of knee OA defined by osteophytes and K-L grade ≥2
  - Independent of obesity
  - Not associated with JSN
- A relationship limited to osteophyte formation may have limited importance
  - **Cartilage loss/JSN** hallmark of established OA
- Is systemic BMD associated with development of JSN and cartilage loss?

Multicenter Osteoarthritis Study (MOST)





- Prospective cohort study of incident T-F knee OA in persons at high risk
- Serial x-rays using protocols sensitive to T-F JSN (2.5 yrs follow-up)
  - Wt. bearing **flexed** PA and lateral knee
- Knee OA onset defined by 1) K-L grade ≥2, 2) Osteophytes and 3) T-F JSN
- Prevalent hip and knee OA excluded
- Analyses of baseline BMD and incident OA adjusted for age, gender, BMI, smoking, physical activity, knee injury, bone antiresorptive use

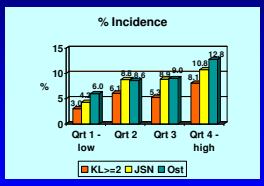
(Nevitt, Arth Rheum, 2007s)

Multicenter Osteoarthritis Study

Percent of knees developing x-ray T-F OA by gender-specific quartile of BMD

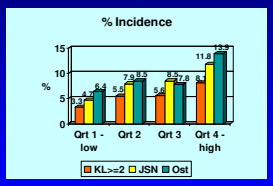
Knees without OA (KL = 0, 1) at baseline (n = 2,275)

Femoral neck (FN) BMD



P for all trends < 0.002

Whole body (WB) BMD



P for all trends < 0.008

(Nevitt, Arth Rheum, 2007s)

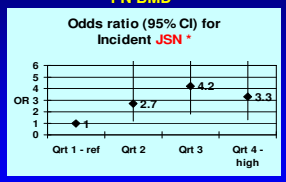
* Increase in any TF location

Multicenter Osteoarthritis Study

ORs for JSN by quartile of BMD, baseline KL grade = 0

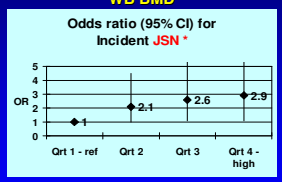
Knees with KL = 0 at baseline (n = 1,670)

FN BMD



P for trend < 0.001

WB BMD



P for trend < 0.001

(Nevitt, Arth Rheum, 2007s)

* Increase in any TF location

Multicenter Osteoarthritis Study

BMD and T-F cartilage loss

- Methods for cartilage loss
  - Serial MRI on 1.0 T extremity scanner (2.5 yrs follow-up)
  - SQ assessment of T-F cartilage loss (WORMS)
    - Increase in WORMS score BL – 2.5 yrs
  - 377 knees with baseline KL= 0-1

(OARSI 2008 – poster #318)

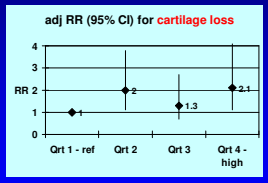
WORMS cartilage grades (Peterfy, 2004)

Multicenter Osteoarthritis Study

Relative risk for T-F cartilage loss by quartile of BMD

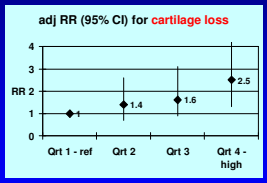
Knees without OA (KL = 0, 1) at baseline (n=377)

FN BMD



P for trend = 0.084

WB BMD



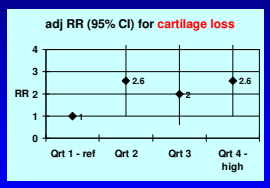
P for trend = 0.001

Multicenter Osteoarthritis Study

RR for T-F cartilage loss by quartile of BMD in KL = 0 knees

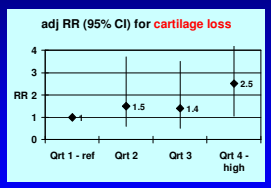
Knees with KL = 0 at baseline (n=255)

FN BMD



P for trend = 0.027

WB BMD



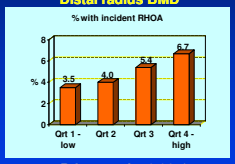
P for trend = 0.049

Multicenter Osteoarthritis Study

High BMD and Incident Hip OA?

- Study of Osteoporotic Fractures (SOF)
- White women age ≥ 65 (n = 5656) followed for 8 years for incident x-ray hip OA (JSN + Ost)

Distal radius BMD



P for trend < 0.001*

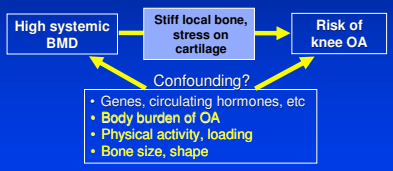
Qrt4 vs Qrt1: **OR 1.9** (1.3, 2.8)*

(Nevitt, Arth Rheum, 2000s)

* All models adjusted for age, BMI, height

Conclusions?

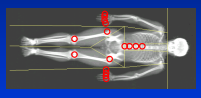
- High BMD phenotype increases the risk developing knee and hip OA, including early JSN and cartilage loss at the knee
- How is systemic BMD (BMD at distant sites) related to initiation and development of OA in a knee?



- What's in an arealBMD measure?

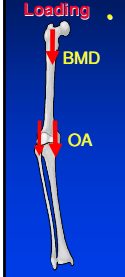
Body burden of OA

- Bone hypertrophy secondary to OA (osteophytes, sclerosis, buttressing, calcification)
  - Included in DXA scan field, increases aBMD



  - High BMD at distant sites may reflect a systemically increased risk of OA (total body burden)
    - Difficult to study only persons with NO OA
    - Unlikely to explain radius BMD and hip OA

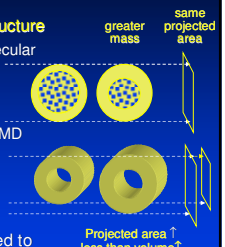
Physical activity, loading



- Loads on bone and joint
  - Bone mass adapts to, and reflects, loads on skeleton (Wolff's law)
    - Is BMD a marker for loading history?
  - Abnormally high loads on knee joint a major risk factor for knee OA
  - Does BMD - knee OA association reflect high loads on bone and joint over time?
    - BMI and physical activity poorly capture loading conditions in knee and hip

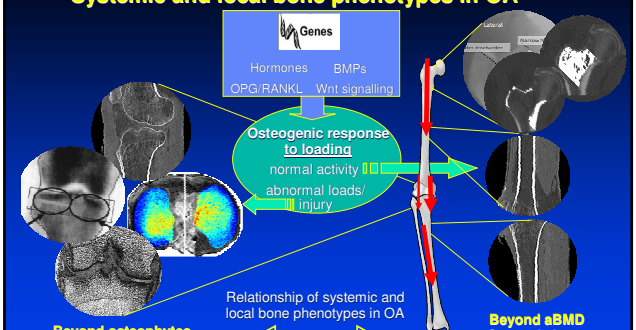
Bone size/geometry/distribution

- DXA aBMD a 2D projection of a 3D structure
  - Relative contribution of cortical vs trabecular bone?
    - Thicker cortices = ↑ areal BMD
  - aBMD overestimates true volumetric BMD proportional to increase in bone size (Carter, JBMR, 1992)
    - Larger bones = ↑ areal BMD



- New imaging data (including 3D) needed to provide more complete description of OA skeletal phenotype
  - bone size, geometry, distribution, strength

Systemic and local bone phenotypes in OA



Screening for knee OA risk using aBMD?

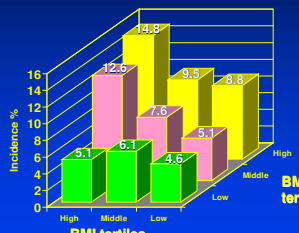
- Despite limitations of DXA aBMD

  …or perhaps because of them…

  it may be useful for risk stratification

Hip BMD, BMI, Risk of T-F JSN Knees with KL=0-1 at baseline

- BMD and BMI are independent risk factors for onset of knee OA



– Selection for studies of OA onset

– Risk-based guidelines for prevention

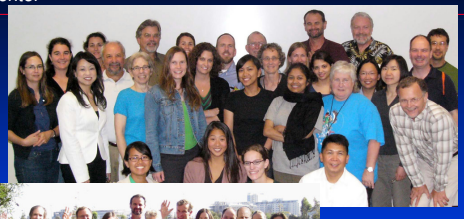
Multicenter Osteoarthritis Study

MOST

Collaborators

Coordinating Center

Colleagues at UCSF



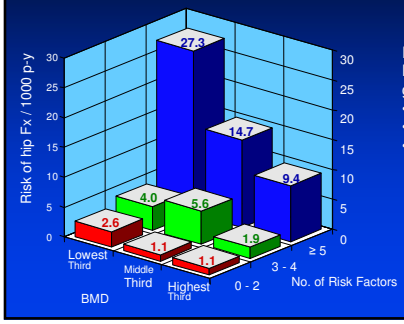
OAI

MOST

Family

THANK YOU

Risk factors for hip fracture independent of BMD



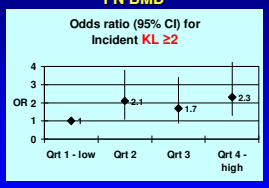
Risk factors independent of BMD used in risk-based Tx guidelines for osteoporosis
- NOF
- IOF
- FRAX

(Cummings, Nevitt, NEJM 1995)

ORs for incident KL ≥ 2 and JSN by quartile of FN BMD

Knees without OA (KL = 0, 1) at baseline

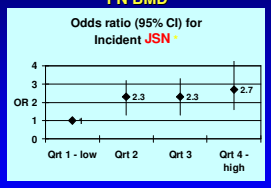
FN BMD



P for trend < 0.001

(Nevitt, Arth Rheum, 2007s)

FN BMD

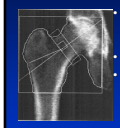


P for trend <0.001

* Increase in any TF location

Multicenter Osteoarthritis Study

SOF hips without radiographic OA



- In SOF, have evaluated both areal hip BMD and hip geometry as predictors of incident x-ray hip OA (Javaid, Lane)
  - Geometry from DXA scans using HSA
- White women age > 65, serial hip films 8 yrs apart (n=4,913)
- Hip BMD and femoral neck width independently predict incident RHOA (JSN and Ost)
  - RR per SD of hip BMD: 1.6 (1.3, 2.0)
  - RR per SD of FN width: 1.5 (1.2, 1.8)
- Excess loads leading to OA may cause cortical thickening, bone expansion
- Or skeletal phenotype
  - Genetic predisposition to large bones
  - Bones that hypertrophy in response to high loads
- Greater size of tibial plateau associated with early MRI changes of knee OA
  - Cartilage defects
  - Mensical damage

References

Research Agenda

- **How is systemic BMD (BMD at distant sites) related to what goes on in a knee developing OA?**
- Apply noninvasive techniques to document early periarticiular bone changes, including nonxray based definitions of early OA
- Identify early local bone changes that precede development of OA
- Determine relationship of systemic skeletal phenotype (mass, metabolism) to these early local changes
  - Use 3D imaging methods to better characterize systemic skeletal phenotype (size, geometry, density, mass)
- Identify genetic factors that influence both systemic phenotype (e.g. size of bone envelope) and local bone/cartilage response to mechanical stress e.g. WNT
- Modifiable pathways
- Better studies of role of loading on both bone and joint