WHEN BONE DENSITY IS NOT ENOUGH:
CLINICAL IMPLICATIONS OF BONE MICROSTRUCTURE

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John P. Bilezikian, MD
College of Physicians and Surgeons
Columbia University
New York, NY USA
John P. Bilezikian, M.D.

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Outline

• The importance of Dual Energy X-ray Absorptiometry (DXA) in clinical medicine
• The shortcomings of DXA
• New technologies are helping to solve vexing clinical problems
  – Primary Hyperparathyroidism
  – Diabetes Mellitus
  – Racial differences in fracture risk (Asians vs Caucasians)
How did we diagnose osteoporosis before DXA (< 1986)?
The Physical Signs of Severe Osteoporosis


Photo courtesy of the National Osteoporosis Foundation
The Vertebral Fracture
Bone Mineral Densitometry became a clinical measurement tool for bone mass around 1986

Safe
Accurate
Precise
Normative population databases
Correlates with fracture risk
Relationship Between BMD and Fracture Risk in Untreated Patients

Reduced bone mass is a key risk factor for the fragility fracture.

Reduced bone density reflects reduced bone strength.
BMD: A Continuum of Risk

Osteoporosis  Low bone mass  Normal

Are these individuals at risk?

BMD, bone mineral density

Population BMD Distribution, Fracture Rates, and Number of Women With Fractures

Fracture rate

Fracture per 1000 Person-Years

BMD T-Scores (Peripheral)

BMD distribution
Fracture rate
No. of women with fractures

No. of Women With Fractures

Most osteoporotic fractures occur in individuals who do not have osteoporosis, as measured by bone densitometry.
Fractures and the T-score:

CONFOUNDER!

The are many millions of individuals with osteopenia who will not fracture!

It is not cost-effective to treat these osteopenic individuals whose risk of fracture is very low.
Beyond DXA: FRAX

- Age
- BMI*
- Prior fracture
- Current corticosteroid use
- Family history of hip fracture
- Current smoker
- >3U alcohol/d
- Secondary cause(s) such as RA

*BMI or BMD can be used (if BMI is <21) — but not both.
How to deal with the patient whose bone density is in the osteopenic range (AACE Guidelines)

<table>
<thead>
<tr>
<th>T-score</th>
<th>Therapy decision</th>
</tr>
</thead>
</table>
| -2.5 or below | High risk  
Treat                                 |
| -1.5 to -2.5 | Intermediate risk  
Treatment is needed if other risk factors are present  
Fractures  
F. Hx of hip fx  
Age (>70)  
Steroids  
Weight  
Smoking  
Alcohol (> 3 units/day)  
Secondary Causes |
| Above -1.5  | Low risk  
General preventive measures              |
WHY FRAX IS NOT PERFECT!

- Bone turnover not considered
- Other contributors to bone strength not considered
- Lumbar spine, distal radius not considered
- Rate of bone loss not considered
- Secondary causes, besides RA, de-emphasized
- Long term risk not considered
- Fall risk not considered
BEYOND DXA AND FRAX

• DXA is helpful
• FRAX adds to the risk profile and, in fact, can be used without DXA!
• But, there are situations where neither DXA nor FRAX gives us the information that we need.
• We need a technology that gives insight into skeletal microstructure to assess more completely who is at risk for fracture
DXA is helpful
FRAX adds to the risk profile and, in fact, can be used without DXA!
But, there are situations where neither DXA nor FRAX gives us the information that we need.
We need a technology that gives insight into skeletal microstructure to assess more completely who is at risk for fracture

**EXAMPLES:**
- Primary hyperparathyroidism
- Diabetes/obesity
- Chinese American Women
A common endocrine disorder characterized by incompletely regulated, chronic, excessive secretion of parathyroid hormone from one or more parathyroid glands.

Primary Hyperparathyroidism is associated with hypercalcemia and elevated levels of parathyroid hormone.
The densitometric signature of primary hyperparathyroidism in the modern era

Bone Mineral Density: % of Expected

* Differs from radius, p<.05

Silverberg, Bilezikian et al. JBMR, 1989
Based upon BMD and bone biopsy data, expectations for fracture incidence in PHPT:

- Vertebral sites
- Non-vertebral sites
But......
Fracture Risk in Primary Hyperparathyroidism

Khosla et al, J Bone Min Res 14:1700-1707, 1999
Mosekilde L. Clin Endocrinology, 2008
Fracture risk in PHPT

• 9 references: 1988-2006 (5 from Northern Europe)
• Mostly cross-sectional
• Relative risk of non-spine and spine fractures increased generally but not in all studies
HRpQCT (Xtreme CT)

- 3-D stack of 110 high resolution slices
- ~ 3 min scan time
- <4 µSv radiation
- Reproducibility:
  - Density: 0.7-1.8%
  - Structure: 1.2-5.2%

Boutroy et al. JCEM 2005. 90(12):6508-15
Hansen S et al. Parathyroidectomy and changes by HRpQCT. J Bone Miner Res 2012;27:1150-1158

- 27 subjects with PHPT vs 31 controls
- Well matched
- Mostly postmenopausal: 14 and 18 years
- Hx of fractures 9/27 (PHPT) and 6/31 (C)
- HRpQCT performed at baseline and 1 year after PTX or for controls 1 year thereafter
Baseline data: PHPT vs Controls (p<0.05)

<table>
<thead>
<tr>
<th>Index</th>
<th>RADIUS</th>
<th>TIBIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV BMD</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Cort BMD</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Trab BMD</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Trab BV/TV</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Tb.N</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Tb. Th</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tb. Sp</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Failure Load</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>
HRpQCT in PHPT
(Stein E, Silva BC et al. J Bone Miner Res, 2013)

Matched Control  PHPT
Trabecular and cortical indices are reduced at radius and tibia in Asymptomatic PHPT

Stein E, Silva BC et al. HRpQCT in PHPT, J Bone Miner Res, 2013
Microstructure as analyzed by Individual Trabecula Segmentation (ITS)- Guo and Liu, 2010

• ITS can differentiate between plate- and rod-like trabeculae type
  – More plates are associated with greater strength
ITS in Primary Hyperparathyroidism
Stein E, Silva BC J Bone Miner Res, 2013

Matched Control
Primary Hyperparathyroidism

Green: horizontal plates (good)
Red: vertical plates (bad)
The Conundrum in Primary Hyperparathyroidism

- Lumbar spine BMD in PHPT is discordant with fracture data
- HRpQCT indices in PHPT are concordant with fracture data
- DXA is readily available
- HRpQCT is not

Needed: A readily accessible method that can give information about skeletal microstructure
TRABECULAR BONE SCORE (TBS)
The general idea!

Identify each single Tree?

Not possible

What about identifying all clearings?

Much easier
TBS Simplified Principle

TBS A > TBS B
Trabecular Bone Score

- Predicts fracture independent of BMD
- Osteopenic patients with a low TBS [A] have a higher risk of fracture than osteoporotic patients with a high TBS [B]
- ~3 x risk of fracture for lowest vs. highest tertile of TBS
- Approved as a device by the FDA in 2012. Software available and easily installed

Fracture incidence in TBS Tertiles by BMD category

Manitoba Study
N = 29,407 women

Hans, Leslie et al. JBMR 2011
Romagnoli E, Cipriani C, Nofrani I, et al. TBS in postmenopausal women with PHPT. Bone 2012:154-159

Adapted from Table 2

<table>
<thead>
<tr>
<th>Index</th>
<th>VF+ (n=29)*</th>
<th>VF- (n=44)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>67.6 ± 8.2</td>
<td>61.0 ± 8.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>YSM (yrs)</td>
<td>19.2 ± 10.3</td>
<td>11.5 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.4 ± 6.2</td>
<td>24.8 ± 3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>TBS</strong></td>
<td><strong>1.14 ± 0.10</strong></td>
<td><strong>1.22 ± 0.10</strong></td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>LS BMD</td>
<td>-2.29 ± 1.2</td>
<td>-1.78 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>FN BMD</td>
<td>-1.85 ± 1.01</td>
<td>-1.88 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>1/3 RAD</td>
<td>-2.34 ± 1.2</td>
<td>-1.73 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*24/29 Grade 1 Fx; ** Nl > 1.30
Densitometric and TBS data in 22 PHPT postmenopausal women (Silva et al, J Clin Endo Metab, 2013)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PHPT (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td><strong>1.24 ± 0.02</strong></td>
</tr>
<tr>
<td>L1-L4 T-Score</td>
<td>-1.0 ± 0.4</td>
</tr>
<tr>
<td>Total hip T-Score</td>
<td>-1.1 ± 0.3</td>
</tr>
<tr>
<td>Femoral neck T-Score</td>
<td>-1.4 ± 0.3</td>
</tr>
<tr>
<td>1/3 radius T-Score</td>
<td>-1.3 ± 0.4</td>
</tr>
<tr>
<td>Osteoporosis at any site</td>
<td>11 (50%)</td>
</tr>
</tbody>
</table>

Microarchitecture partially degraded

- <1.2 = degraded
- 1.2 – 1.35 = partially degraded
- >1.35 = normal

<table>
<thead>
<tr>
<th>L1-L4 T-score classification</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Normal</td>
<td>12 (53)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>L1-L4 TBS classification</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degraded</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Partially degraded</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (27)</td>
</tr>
</tbody>
</table>
Moving the field forward with a “new” hypothesis

Primary hyperparathyroidism, even when presenting as an asymptomatic disorder, is characterized by compromised cortical and trabecular compartments and increased fracture risk.
Skeletal evaluation, in addition to DXA will be recommended in the evaluation of PHPT: VFA, TBS or vertebral X-rays.

Risk Factors for Osteoporosis

- Age
- Family (genetics)
- The menopause
- Certain medications like glucocorticoids
- Other diseases (rheumatoid arthritis, COPD, Type 1 Diabetes mellitus)
- Nutrition (anorexia, vitamin D deficiency)
- Lifestyle issues (smoking, excessive alcohol, lack of exercise)
Risk factors for Osteoporosis

- Not on most lists:

- Type 2 Diabetes mellitus
A paradox: Type 2 Diabetes Mellitus should protect against osteoporosis

- Protective Factors:
  - Average or higher BMD than age-matched controls
  - Greater weight in general
In Type 2 Diabetes Mellitus, BMD is higher

Study of Osteoporotic Fractures (n=9654 women, ≥65 yo)
BMD in T2D:

- 5% higher at radius
- 5% higher at calcaneus
- 3% higher at femoral neck

With or without insulin, adjusted for body size

T-scores in T2D are 0.3–0.8 higher than those in controls
Expectations of fracture risk in Diabetes Mellitus based upon bone mineral density

Should be lower than age- and weight-matched controls
Type 2 Diabetes

• Expectation:
  – Lower Fracture Risk
  
  but....

• Fracture risk is higher
Type 2 Diabetes and Fracture Risk
Meta-analyses

- Vestergaard et al. 2007 (8 Studies)
  - Age-adjusted
  - By BMD alone, the RR would be expected to be lower, approximately 0.77
  - But RR for hip fracture is higher, 1.38 (1.25-1.53)

- Janghorbani et al. 2007 (8 Studies)
  - Adjusted for multivariables
  - Hip fracture RR=1.7 (1.3-2.2)
  - Any fracture RR=1.2 (1.01-1.5)
Increased Fractures are at Multiple Sites in T2D

WHI (n=93,676; 7 years follow-up)
RR for fracture in T2D:

• Hip 1.41
• Foot 1.44
• Upper arm 1.30
• Ankle 1.34
• Spine 1.28
• Forearm 0.98
Duration of T2D is associated with higher risk of hip fracture: Scottish Registry Study:  

Entire Cohort:

Men: **RR 0.97** (0.92-1.02)  
Women: **RR 1.05** (1.01-1.10)

T2D duration > 7 years:

Men: **RR 1.25** (1.08-1.45)  
Women: **RR 1.55** (1.38-1.75)

*In T1 DM: Men: RR 3.28 (2.52-4.26)  
Women: RR 3.54 (2.75-4.57)
Question: Given that BMD is higher in T2D, can we use it to predict fracture?
3 prospective cohorts:

- SOF
- MrOS
- Health ABC

Answer: Yes, BMD is predictive of fracture risk in T2D, *But* the relationship is different

Schwartz JAMA 2011
BMD Can Predict Fracture in T2D

But for a given T-score, T2D will have a higher fracture risk

T score difference of 0.6 for same fracture risk
Can the FRAX Score, as currently constituted, be used reliably in T2D?*

- BMD (femoral neck T-score)
- Age
- Gender
- Race
- BMI
- Fracture history
- Parental history of hip fracture
- Current smoker
- Recent corticosteroid use
- Rheumatoid arthritis
- 3+ alcohol drinks/day

* Diabetes is not listed as a clinical risk factor!
FRAX is Predictive of Fracture Risk in T2D, But the Relationship is Different

For a given FRAX score, T2D will have a higher fracture risk

For a given FRAX score, fracture risk is higher than predicted in T2D

Schwartz JAMA 2011
Type 2 Diabetes and Fracture

- For a given BMD, fracture risk in Diabetes Mellitus is greater.

- For a given FRAX score, fracture risk in Diabetes Mellitus is greater.
There must be factors that account for fracture risk in T2D that are not captured by either BMD or FRAX!
Why in T2D is there an increase in fractures?
Possible contributing factors for increased fracture risk in T2 Diabetes Mellitus

- Contributing Factors:
  - Falls?
  - TZDs?
  - Skeletal abnormalities?
  - Fat?
Possible reasons for increased falls in T2D

- Peripheral neuropathy (impaired balance, gait)
- Poorer Vision (Retinopathy)
- Knee and hip osteoarthritis
- Cardiovascular (CHF and arrhythmias)
- History of CVA
- Hypoglycemia (with insulin use)
- Low vitamin D
Higher Risk of Falls in T2D

- Finland 20-92 y.o.: 1.6 (1.1-2.4) for insulin tx, 3.3 (1.4-8.0)
- Rotterdam 55+:
  - ♀: 0.6 (0.6-1.2)
  - ♂: 1.4 (0.9-2.1)
- St. Louis AA 70+ y.o.: 1.8 (1.1-3.2)
- NHANES 60+:
  - ♀: 1.6 (1.2-2.1)
  - ♂: 1.2 (0.8-1.8)
- EPESE 65+: 1.4 (1.0-1.8)
- SOF 65+:
  - ♀: 1.5 (1.1-2.0)
  - Insulin tx: 4.0 (2.2-7.0)
Fall Risk: A1C and Insulin Use

The graph shows the probability of at least one fall per year as a function of Hemoglobin A1C (%). The graph compares insulin users (solid line) and non-insulin users (dashed line). The probability decreases with increasing A1C for both groups, but the rate of decrease is greater for insulin users compared to non-insulin users.
But when studies adjusted for falls, T2D was still associated with increased fracture risk.

All accounted for falls:
- WHI Bonds 2006
- Health ABC Strotemeyer 2005
- SOF Schwartz 2001
- Rotterdam study de Liefde 2005

Falls are not the whole story
Possible contributing factors for increased fracture risk in T2 Diabetes Mellitus

- Contributing Factors:
  - Falls?
  - TZDs?
  - Skeletal abnormalities?
  - Fat?
TZDs are likely to shift bipotential bone marrow precursor cells from the osteoblast lineage tract to the adipocyte lineage tract.
Rosiglitazone increased fracture risk in women

*P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

Kahn Diabetes Care 2008
TZDs and Fracture

TZDs should not be used in women at higher risk of fracture
But, most of the fracture data in diabetes were acquired before TZDs were available.

TZDs increase fracture risk.

TZDs are not the whole story.
Diabetics Have Multiple Risk Factors for Poor Skeletal Health

- **Contributing Factors:**
  - Falls
  - TZDs
  - *Abnormal Skeletal Properties*
    - *Reduced Turnover?*
    - *Abnormal Biomechanics?*
    - *Reduced Bone Quality?*
Reduced Bone Formation in T2D

The circulating bone formation marker, osteocalcin, is reduced

By bone biopsy, bone formation rate is low
  T2D (n=6) compared with premenopausal women
    Krakauer et al 1995

  T2D (n=5) compared with controls
    (n=5), postmenopausal women
    Manavalan et al 2012
Histomorphometric Bone Formation is Low in T2D

Manavalan JCEM 2012
Low Bone Formation in T2D

Osteocalcin is decreased

Gerdhem OI 2005, Dobnig JCEM 2006,
Yamamoto JCEM 2012

Control

T2D

Krakauer Diabetes 1995, Manavalan JCEM 2012
Sclerostin, a product of the osteocyte, inhibits bone formation.
Sclerostin is Increased in T2D

Sclerostin may suppress bone formation in T2D

Gennari JCEM 2012
Diabetics Have Multiple Risk Factors for Poor Skeletal Health

- **Contributing Factors:**
  - Falls
  - TZDs
  - **Abnormal Skeletal Properties**
    - Reduced Turnover
    - Abnormal Biomechanics?
    - Reduced Bone Quality?
Skeletal Geometry is Worse in T2D

- **By BMD:** femoral neck aBMD is higher, but femoral neck strength is lower relative to load  
  Ishii J Clin Endocrinol Metab 2012

- **By QCT:** Trabecular BMD is higher but load to strength ratio for hip fracture is not enhanced  
  Melton J Clin Endocrinol Metab 2008

- **By pQCT:** Cross sectional area and bone bending strength at cortical sites are lower  
  Petit J Bone Miner Res 2010

Despite higher areal BMD, biomechanical indices are worse
Skeletal Abnormalities in T2 Diabetics Mellitus

- Reduced Turnover
- Abnormal Biomechanics
  - Reduced Bone Quality?
    - Cortical
    - Trabecular
    - Matrix (AGEs)
    - Marrow fat
Extreme CT: Is Microarchitecture Abnormal in T2D?

High Resolution
Peripheral
Quantitative
Computed Tomography

82 microns
Cortical Porosity May be Increased in T2D

- 19 T2D women vs 19 controls
- Cortical porosity was 124% higher in T2D at radius

Control  Diabetes  Diabetes + fracture

Burghardt JCEM 2010
### Cortical Porosity: Higher in T2D with fracture

#### Postmenopausal women

<table>
<thead>
<tr>
<th></th>
<th>No diabetes</th>
<th>T2 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No fracture</td>
<td>History of fracture</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Distal radius</td>
<td>1.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Distal tibia</td>
<td>4.3%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

*p<0.05 compared to T2D without fracture
Standard HRpQCT variables did not differ by diabetes or fracture status

Patsch JBMR 2013
Cortical Porosity May be Increased in T2D With Fragility Fractures

Distal Radius

Changes in cortical bone are captured by HRpQCT in T2D with fractures

Patsch JBMR 2013
Skeletal Abnormalities in T2 Diabetes Mellitus

- Reduced Turnover
- Abnormal Biomechanics
  - Reduced Bone Quality
    - Cortical
    - Trabecular?
    - Matrix (AGEs)?
    - Marrow fat?
TBS predicts fracture risk in Diabetes (Leslie et al. JCEM, 2012)
TBS Predicts Osteoporotic Fractures in Diabetes

In Diabetes:
- Higher BMD but lower TBS
- TBS predicted fracture, independent of BMD: adjusted hazard ratio of 1.27 (1.10-1.46)

TBS captures a larger portion of the diabetes-associated fracture risk than BMD

Leslie et al JCEM, 2013
Skeletal Abnormalities in T2 Diabetics Mellitus

- Reduced Turnover
- Abnormal Biomechanics
  - Reduced Bone Quality
    - Cortical
    - Trabecular
    - Matrix (AGEs)?
    - Marrow fat?
Advanced Glycation Endproducts (AGEs)

Glucose + amino acid protein

↓

Schiff’s base

↓

Amadori product

Oxidative pathway

Non-oxidative pathway

CML

Pentosidine

pyrraline

“Browning” meat

“Browning” bone

Sections of in vitro glycated bone tissue showing a progressive increase in tissue fluorescence (excitation/emission: 370 nm/440 nm) with time of incubation (a: control; b: 3 days; c: 11 days; d: 38 days). The increased incubation period leads to a more homogeneous glycation of cortical bone microstructure. Figure adapted from Ref. 61.
- Type 1 collagen: scaffolding and toughness
- Enzymatic cross-linking: stiffness
- Non-enzymatic cross-linking (AGE):
  - accumulate with age and glucose
  - slow bone turnover
  - brittleness
  - decrease bone strength independent of BMD
**AGEs are associated with fractures**

- 765 postmenopausal women followed for 5 years; *HR for 1 SD increase in urinary pentosidine 1.18 for vertebral fracture and 1.20 for long bone and vertebral fracture*. Tanaka J Bone Miner Res 2011

- 76 T2D women had *higher serum pentosidine levels if they had vertebral fracture (OR 2.50, CI: 1.09-5.73)*. Yamamoto J Clin Endocrinol Metab 2008

- Health ABC: 1,000 patients followed for 7.5 years, *urinary pentosidine was associated with increased clinical fracture incidence in T2D (RH 1.42, 1.10-1.83)*. Schwartz J Clin Endocrinol Metab 2009

**Findings were independent of BMD**
Measuring Bone Strength *in vivo*

Microindentation
Microcracks Created by Microindentation

Diez-Perez et al. JBMR 2010
Bone Material Strength (BMS) in T2D

- Postmenopausal 30 T2D and 30 controls
- T2D: 77.7 ± 1.9 vs control: 85.2 ± 1.9, p=0.005
- Persisted after adjusting for higher BMI
- Average HbA$_1c$ over past 10 years correlated inversely with BMS

Farr et al JBMR, 2013
Other Aspects Of Bone Strength Not Captured By DXA

- Impaired bone formation
- Skeletal geometry
- Cortical porosity
- AGEs
- Bone marrow fat composition
Fractured Diabetics Have Altered Bone Marrow Fat Saturation

↓ unsaturation and ↑ saturation

Patsch JBMR 2013
Increased Fracture Risk in Diabetes Mellitus

- Multifactorial skeletal factors
  - BMD
  - Bone turnover
  - Microarchitectural
  - Bone Matrix
  - Material Properties
  - Others?
Chinese women have lower bone density than Caucasian women

- As determined by DXA

BMD Differences Between Chinese & Caucasian Women

Expectation

• Chinese (and other Asian) women should have higher fracture risk than Caucasian women because their BMD is lower

but.......
Chinese and other Asian women have a lower rate of hip fracture than Caucasian women.

Barrett-Connor et al. JBMR 2005; 20: 185-194
Framing the paradox as a question:

• Why do Chinese (and other Asian women) fracture less often when their lower bone density predicts they will fracture more often?
One possibility:
DXA-based BMD is
giving a falsely lower value because
it is influenced by bone size

• DXA, an areal BMD (g/cm²), …
  – Overestimates BMD if bones are large
  – Underestimates BMD if bones are small

• When bone size is taken into account…….

• Differences between the smaller Chinese women and the larger Caucasian women are reduced
Adjusted BMD by DXA


Adjustments for age, weight, age of menarche, sport index, tobacco use, PTH and 25-hydroxy vitamin D levels
Caucasian

29 yr-old Caucasian
Hgt- 169 cm
Wgt- 67 kg
DXA:
  T Score- Hip 1.16
  T Score- Radius 1.28
  T Score- L Spine 1.21

Chinese

31 yr-old Chinese
Hgt- 163 cm
Wgt- 56 kg
DXA:
  T Score- Hip 0
  T Score- Radius 0.18
  T Score- L Spine 0.72
Bone Area (mm$^2$)

Bone Area

P < 0.001
P = 0.01

10-15% smaller area in Chinese compared to Caucasian women
Trabecular bone density 22% higher and cortical bone density 5% higher in Chinese compared to Caucasian women
Trabecular thickness 21% higher in Chinese compared to Caucasian women
Cortical thickness 23% and 9% greater in Chinese compared to Caucasian women radius and tibia respectively.
29 years old Caucasian
Height 169 cm
Weight 67 kg
T Score-Hip 1.16
T Score-Radius 1.28
T Score-Lumbar Spine 1.21

31 years old Chinese
Height 163 cm
Weight 56 kg
T Score-Hip 0
T Score-Radius 0.18
T Score-Lumbar Spine 0.72
Caucasian

Plates

Rods

Chinese
Individual trabecular analyses
Chinese Women have stronger bone because of

- Higher Amount of Plate-Like Bone Volume
- More Plate-Like Trabeculae
- More Plate-Rod, Plate-Plate, and Rod-Rod Connections
- Thicker and Larger Trabecular Plate and Thicker Rod
Conclusion

- Chinese women have stronger bones than Caucasian women because their skeletal microstructure is better oriented to withstand mechanical stress.
- These features are appreciated only by analyzing skeletal microstructure.
Beyond DXA: added clinical and scientific value of new approaches

- FRAX
- Vertebral Fracture Assessment (VFA)
- High resolution imaging; compartmental analysis and further adaptations by FEA and ITS
- Trabecular Bone Score
- Analysis of matrix properties (AGEs and Microindentation analysis)
Beyond DXA: Conclusion

New imaging technologies have helped to delineate microstructural abnormalities of bone, accounting for fracture risk in a number of disorders for which DXA alone is not sufficient.