Bone Micro-Architecture Assessed by TBS Predicts Hip, Clinical Spine and All Osteoporotic Fractures Independently of BMD in 22234 Women aged 50 and Older:

The Manitoba Prospective Study

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In EPISEM, 6’862 PM white women ≥70 years, randomly selected from population based listing. Mean Follow-up of 3.2 yrs. 678 OP fractures (hip, distal forearm, proximal humerus)

BMD distribution

- Fracture rate
- No of women with fractures

Hans, Krieg et al. 2006, Philadelphia, USA  ASBMR
Trabecular Bone Score: a new parameter

Trabecular bone tissue

3D microarchitecture (porous material)

Φ: porosity

TbSp: pore size

2D plain projection (grey level image)

Pothuaud, Carceller, Hans et al. Bone 2007
TBS: Principles...

Well structured microarchitecture

Poorly structured microarchitecture

2D projection Processus as seen on DXA

experimental variogram

\[ V'(k) = \langle \left[ I(\bar{P}_0 + \text{lag}.k.\bar{u}_\theta) - I(\bar{P}_0) \right]^2 \rangle_{(\bar{P}_0, \theta)} \]

Many local grey level variations pixel by pixel ≠ Few local grey variations then at some point important one

TBS = Slope at the origin
What is TBS measuring: simulation

TBS is significantly correlated to 3D bone micro-architecture:

- Connectivity (connD) : $r^2=0.72$
- Trabecular Number (TbN): $r^2=0.71$
- Trabecular Space (TbSp): $r^2=0.53$

Low TBS

low { connD, TbN }
high TbSp
« weak micro-architecture »

High TBS

high { connD, TbN }
Low TbSp
« good micro-architecture »

Source: Pothuaud L., Carceller P., Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: Applications in the study of human trabecular bone microarchitecture. Bone 2008 Apr;42(4):775-87
What is TBS measuring: ex-vivo

- 40 vertebrae / 28 vertebrae
- Acquisitions μCT (93µm) and reconstruction 3D
- Calculation of Parfitt parameters

- Acquisition DXA Prodigy with dedicated positioner
- Calculation of TBS from DXA image
- Compression test

- Correlations TBS (DXA), Parfitt’parameters, Ultimate strenght

\[ \text{ConnD (r}^2=0.74) \]
\[ \text{TbN (r}^2=0.58) \]
\[ \text{TbSp (r}^2=0.42) \]

Ultimate strenght = 0.5

Independently of DXA BMD
Diagnostic value: All BMD zone

Objective: Evaluate the ability of TBS to discriminate Fracture from non fracture subjects independently of BMD

Design: Case control, retrospective multicenter study

Study population:
- Caucasian postmenopausal women
- Age from 50 to 90 years

Method:
- 2 clinical centers, inclusion / exclusion
- cross-calibration
- Central review of DXA scans
- Calculation of TBS L2-L4

Results:
- Total population (n=135)
  - 45 fracture subjects (inc. 20 VF)
  - 90 age and BMD matched controls

Source: Hans et al. JCD 2009 In-Press
Study objectives

• The aim of our study was to prospectively evaluate the ability of lumbar spine TBS to predict osteoporotic fractures.

• Check if the prediction is independent of the site matched and non matched BMD

• Verify if the combination of TBS and BMD do have an added effect on the prediction
Material and Method

• 22,234 women age 50 years and older were identified in a database containing all clinical results for the Province of Manitoba, Canada.

• All had baseline hip and spine DXA

• Health service records were assessed for the presence of non-trauma osteoporotic fracture codes subsequent to BMD testing.

• Lumbar spine TBS was derived by the Bone Disease Unit, University of Lausanne, for each spine DXA examination using anonymized files (blinded from clinical parameters and outcomes).
Practically
Material and Method con’t

• **Statistics:**
  
  – Cox proportional hazard regression to model the hazard of first hip, spine or any osteoporotic fracture (hip, clinical spine, humerus, forearm).

  – Age-adjusted HRs for fracture per SD decrease in TBS and/or BMD.

  – Incremental gain in prediction information when TBS was added to age and BMD was assessed using the log-likelihood ratio test (LLR).
Results

The numbers of fractures during mean 4.6 y of follow up were:

- All osteoporotic* 946 (4.3%),
- Hip 194 (0.9%)
- Clinical spine 297 (1.3%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Std.Dev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>65.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Height</td>
<td>160.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Weight</td>
<td>68.9</td>
<td>14.2</td>
</tr>
<tr>
<td>coverage_before (y)</td>
<td>30.9</td>
<td>9.3</td>
</tr>
<tr>
<td>coverage_after (y)</td>
<td>4.6</td>
<td>2.1</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8</td>
<td>5.3</td>
</tr>
<tr>
<td>L14 T (no exclusions)</td>
<td>-1.1</td>
<td>1.6</td>
</tr>
<tr>
<td>L14 Z</td>
<td>0.0</td>
<td>1.4</td>
</tr>
<tr>
<td>NECK T (NHANES8)</td>
<td>-1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>TROCH T (NHANES8)</td>
<td>-1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>TOTAL T (NHANES8)</td>
<td>-1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>TBS_L1</td>
<td>1.136</td>
<td>0.154</td>
</tr>
<tr>
<td>TBS_L2</td>
<td>1.238</td>
<td>0.143</td>
</tr>
<tr>
<td>TBS_L3</td>
<td>1.315</td>
<td>0.134</td>
</tr>
<tr>
<td>TBS_L4</td>
<td>1.273</td>
<td>0.140</td>
</tr>
<tr>
<td>TBS_L1L4</td>
<td>1.240</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Correlation between spine BMD and spine TBS was modest ($r=.32$) and less than correlation between spine and hip BMD ($r=.72$), consistent with a skeletal parameter largely unrelated to BMD.

* = Clinical spine, hip, wrist, humerus
### Clinical Spine Fractures

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Clinical Spine Fractures</th>
<th>Clinical Spine Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR / SD (95%CI)</td>
<td>P</td>
</tr>
<tr>
<td>DXA Hip</td>
<td>1.70 (1.48-1.95)</td>
<td>N/A</td>
</tr>
<tr>
<td>DXA Spine</td>
<td>1.49 (1.31-1.70)</td>
<td>N/A</td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.42 (1.26-1.60)</td>
<td>N/A</td>
</tr>
<tr>
<td>Combined</td>
<td>1.59 (1.39-1.83)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>1.33 (1.18-1.51)</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>1.37 (1.20-1.58)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>1.32 (1.17-1.50)</td>
<td></td>
</tr>
</tbody>
</table>

All models are age adjusted. P value is for improvement in model fit when TBS added to BMD and age.

Spine BMD and TBS predicted Clinical Spine fractures equally well and independently.

Results are still significant when adjusted for: ADG comorbidity score, rheumatoid arthritis, COPD, dementia, diabetes, substance abuse, thyroid disease, BMI, prior osteoporotic fracture.
Clinical Spine Fracture

Age adjusted ROC AUC’s for AP Spine

BMD: 0.672 (SE 0.0088)

TBS: 0.654 (SE 0.0090)

BMD+ TBS: 0.681 (SE 0.0086)

P= 0.0013 BMD versus BMD+ TBS

P< 0.0001 TBS versus BMD+ TBS

P values are from AccuROC and uses the Delong and Delong Method to compare the AUC
## Hip Fractures

<table>
<thead>
<tr>
<th></th>
<th>Hip Fractures</th>
<th>HR / SD (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA Hip</td>
<td>2.98</td>
<td>(2.53-3.51)</td>
<td>N/A</td>
</tr>
<tr>
<td>DXA Spine</td>
<td>1.53</td>
<td>(1.31-1.78)</td>
<td></td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.50</td>
<td>(1.31-1.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXA Hip</td>
<td>2.78</td>
<td>(2.35-3.29)</td>
<td>.0060</td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.24</td>
<td>(1.07-1.43)</td>
<td></td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DXA Spine</td>
<td>1.38</td>
<td>(1.18-1.62)</td>
<td></td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.39</td>
<td>(1.21-1.61)</td>
<td></td>
</tr>
</tbody>
</table>

All models are age adjusted. P value is for improvement in model fit when TBS added to BMD and age.

Total hip BMD was the best predictor of hip fracture but addition of spine TBS significantly improved hip fracture prediction.

Results are still significant when adjusted for: ADG comorbidity score, rheumatoid arthritis, COPD, dementia, diabetes, substance abuse, thyroid disease, BMI, prior osteoporotic fracture.
## All osteoporotic Fractures

<table>
<thead>
<tr>
<th></th>
<th>All Osteoporotic Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR / SD (95%CI)</td>
</tr>
<tr>
<td><strong>Univariate</strong></td>
<td></td>
</tr>
<tr>
<td>DXA Hip</td>
<td>1.79 (1.67-1.93)</td>
</tr>
<tr>
<td>DXA Spine</td>
<td>1.53 (1.43-1.64)</td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.34 (1.26-1.43)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
</tr>
<tr>
<td>DXA Hip</td>
<td>1.70 (1.58-1.83)</td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.23 (1.15-1.31)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
</tr>
<tr>
<td>DXA Spine</td>
<td>1.44 (1.34-1.55)</td>
</tr>
<tr>
<td>TBS Spine</td>
<td>1.23 (1.15-1.31)</td>
</tr>
</tbody>
</table>

All models are age adjusted. P value is for improvement in model fit when TBS added to BMD and age.

Addition of spine TBS significantly improved all osteoporotic fracture prediction.

Results are still significant when adjusted for: ADG comorbidity score, rheumatoid arthritis, COPD, dementia, diabetes, substance abuse, thyroid disease, BMI, prior osteoporotic fracture.
Conclusion

• We have demonstrated that spine TBS predicts fractures (hip, clinical spine and all osteoporotic).

• Furthermore, TBS provided information that was independent of spine and hip BMD.

• Combining the TBS micro-architecture index with BMD from conventional DXA incrementally improved fracture prediction in postmenopausal women.
Femoral neck BMD (T-score NHANES)

Fracture rate per 1000 Person-years

BMD 1 = BMD 2

TBS 1 ≠ TBS 2

No of women with fractures

Fracture rate

BMD distribution

32%

16%

0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5

Femoral neck BMD (T-score NHANES)