TBS IN ROUTINE CLINICAL PRACTICE: PROPOSALS OF USE

THE ADDED-VALUE OF BONE TEXTURE IN OSTEOPOROSIS MANAGEMENT

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If osteoporosis is a multi-factorial disease that is often difficult to accurately diagnose, in recent years, more and more diagnostic tools (BMD, FRAX®, TBS, ...) have been developed that, carefully used, can substantially improve the management of such patients. But combining these clinical indicators is far from simple. It was for this reason that we wrote this document: to provide guidance in how to use them.

TBS iNsight® («Trabecular Bone Score») is one of these tools, now available for routine clinical practice, that allows for refinement of osteoporosis diagnosis – using it, you will come to realize that it is even more effective for secondary osteoporosis. Although its relevance as a predictive (e.g., customization of fracture risk profile) and diagnostic tool is proven and clear, when and how best to use it are not yet totally transparent.

It is necessary to keep in mind that TBS is not intended to replace existing tools, but rather to supplement them and assist clinicians in our medical decisions. You will find that we analyze the TBS relative to BMD and other clinical and physiological information at our disposal.

Given the growing number of TBS users and for clarity reasons, a working group of daily users met. This group of clinicians proposes simple rules of interpretation, resulting from the synthesis of our individual practices and of our consensus (according to the «Delphi ranking» method).

The first section recalls the main contextual factors of osteoporosis and the role of TBS as an independent risk factor. The second section, which forms the core of the document, presents, in 4 tables, basic rules of TBS interpretation, taking into account BMD and clinical risk factors. The final and third section describes nine clinical cases that we encountered for which the TBS influenced our decisions regarding clinical management.

However, please keep in mind that osteoporosis is a complex disease and, despite the many tools at our disposal, clinical judgment always takes precedence. This document is not intended to become the reference book of osteoporosis management, but rather inspirational first steps before the publication of official recommendations by scientific societies.

We took great pleasure in creating this document and sincerely hope that it will help you in your daily practice.

Enjoy your reading!

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PS: The cases presented in Part 3 of this document are inspired by real clinical cases but have been adapted to ensure confidentiality. It is important to note that clinical cases reflect individual practices and do not necessarily reflect official guidelines in force (repayment of drugs, etc...) which may vary from one country to another.
1. Management of osteoporosis

**PATHOPHYSIOLOGY AND EPIDEMIOLOGY OF OSTEOPOROSIS**

*Osteoporosis is a skeletal disease characterized by low bone mass (permanent disruption of bone remodeling) and deterioration of bone microarchitecture.*

These changes produce excessive fragility of the skeleton, leading to the increased risk of fracture. Fragility fractures are located mainly in the upper limbs (proximal humerus and distal radius), spine and proximal femur. Because fractures are the major consequence of osteoporosis, a good understanding of the determinants of fracture risk is essential. Bone strength, one of its major determinants, is dependent both on bone mass, reflected by bone mineral density (BMD), and on bone microarchitecture. In fact, BMD explains only 70-75% of the variance in bone strength, while the rest could be related to other factors such as the accumulation of micro fractures, altered bone microarchitecture, disordered bone remodeling or the influence of extra-skeletal risk factors (the most frequent being endocrine disorders like hyperparathyroidism, hypercortisolism and hypogonadism but also certain treatments, like long-term corticosteroids).

Worldwide, osteoporosis affects approximately 200 million women. It is, mainly in Western countries, a major public health concern that will become increasingly important with the aging population and the rising costs of health care. At age 50, the risk of fracture over the remainder of one’s life is approximately 21% for the hip, 41% for vertebrae, and 13% for the wrist. Even though the incidence of vertebral fractures is highest among these figures, it is clearly underestimated. This is largely due to the asymptomatic nature of nearly 70% of vertebral fractures, the fact that most patients do not undergo spine X-rays, and difficulties detecting moderate vertebral fractures.

**BONE IMAGING IN ROUTINE CLINICAL PRACTICE**

Examination with dual energy X-ray absorptiometry (DXA) is currently the reference technique, the gold standard by which to measure bone mineral density (BMD g/cm²). Preferred measurement sites are the lumbar spine, the proximal femur, and the distal third of the radius (see ISCD recommendations). Its goals are to diagnose osteoporosis and estimate fracture risk.

Other imaging techniques exist but are not used in routine clinical practice for a variety of reasons that include non-applicability of the WHO thresholds, costs, radiation exposure, availability, and feasibility at specific anatomic sites (e.g., quantitative computed tomography, MRI, μCT scanner, ...).

The BMD is crucial, since its decrease is associated with a significantly increased risk of fracture. In 1994, experts from the WHO proposed densitometric classification of osteoporosis based on BMD T-scores. This was only intended for the proximal femur, lumbar spine, and distal third of the radius. The BMD T-score represents the number of standard deviations (SD) between an individual’s BMD value and the average maximum BMD (peak bone mass) measured in young and healthy adults between 20 and 40 years old. Four categories or «zones» have been defined:

- **Normal**: T-score > -1 DS
- **Osteopenia**: -2.5 DS < T-score ≤ -1 DS
- **Osteoporosis**: T-score ≤ -2.5 DS
- **Severe Osteoporosis**: T score ≤ -2.5 DS and the presence of one or more so-called low-energy fractures.

In addition to the T-score, the Z-score is occasionally used. It represents the difference between the patient and the mean value for normal subjects of the same age, sex, and ethnicity, expressed in standard deviations. It is particularly used for children, adolescents and young adults, and premenopausal women. Finally, in the case of a Z-score < -2, screening for possible secondary osteoporosis is required.

These two thresholds, -1 and -2.5 SD, although commonly used in routine clinical practice, do not identify all patients at risk for fracture. The main limitation of using BMD as the only method of fracture risk assessment lies in the overlap (Figure below - Study EPISEM) between the BMD values of subjects with versus without a fracture [5-6].

However, this overlap is expected because osteoporosis is a multi-factorial disease and bone density alone is taken into account here. Degradation of the microarchitecture, another component of bone strength, is not evaluated by measuring BMD.

**BONE TURNOVER BIOMARKERS IN ROUTINE CLINICAL PRACTICE**

To improve the diagnosis and management of osteoporosis, bone turnover biomarkers can be used. They can assess, directly or indirectly, bone development or bone resorption activity [7]. These markers are measured in serum, plasma and urine. Plasma osteocalcin, bone alkaline phosphatase and P1NP (Procollagen Type 1 N-Terminal Propeptide) are specific markers of bone formation. The C and N-terminal telopeptides of type I collagen are specific markers of bone resorption; they are used to assess the rate of bone loss, but also the effectiveness of treatment. The ability to measure these markers has led to major advances in clinical research. Unfortunately, for reasons of availability, cost and reproducibility, biological markers of bone turnover are not commonly measured among non-specialists of bone diseases.

To facilitate the combination of these clinical and radiological data, the FRAX® has recently been developed [9]: this tool calculates the probability of major fractures for a given person over a 10-year period. However, risk factors and BMD being equal, the probability of fracture over ten years varies considerably, being quite different in France, Belgium and Switzerland, for example. In addition, decision-making thresholds have been defined to determine treatment, which also differ from one country to another. Moreover, the FRAX® provides no guidance as to the type of treatment that should be prescribed.
TBS: A BONE TEXTURE ANALYSIS
ASSESSING THE STATE OF BONE MICROARCHITECTURE

Despite the use of BMD, biomarkers and fracture clinical risk factors, many patients at risk for fractures are not detected and many fractures are not explained. **BMD is only an assessment of bone mass.** It does not provide information on bone quality, another key parameter describing bone. In addition, fracture clinical risk factors are, at best, an indirect assessment of bone quality. **One important way to describe bone quality is to assess its microarchitecture.** Bone microarchitecture contributes to the mechanical strength of bone \[10\] and, thus, to its ability to withstand fractures. Indeed, for the same amount of bone, bone structures that are more or less mechanically resistant can be distinguished (few large spans are mechanically weaker than a myriad of fine spans). Bone loss is often accompanied by a deterioration in bone architecture, resulting from a decrease in the number of trabeculae of cancellous bone, increased inter-trabecular distances, and a loss of trabecular connectivity. In addition, a reduction in the thickness of cortical bone and an increase in its porosity accompany trabecular bone loss, resulting in, in particular, fragility of the femoral neck. Osteoporotic bone is, hence, called «porous».

TBS (Trabecular Bone Score) is a texture parameter that can be computed from DXA images, and that quantifies local variations in pixels intensities. TBS is derived from the experimental variogram obtained from the gray levels of a DXA image.

It has been shown that **TBS is related to the structural condition of bone microarchitecture** \[11\-13\]. TBS is strongly, positively correlated with the number of spans and with their connectivity, and negatively with the average size of the spaces between spans \[11\-12\] and with the SMI index \«structure model index» \[13\]. That is to say that a high TBS value means that the bone microarchitecture is dense and well-connected, with little space between spans. Conversely, a low TBS value means that the bone microarchitecture is incomplete, with large spaces between spans. In clinical practice, TBS is calculated in a few seconds, using images obtained during BMD examination along with the software TBS iNsight®, which is installed directly onto bone densitometers.

All studies have shown that **TBS is an osteoporosis fracture risk factor.** It is reversible, quantitative, and yields information independent of BMD, as well as corticosteroid intake, rheumatoid polyarthritis, and prevalent fracture after 50 years of age \[27\]. TBS can therefore be used as a risk factor for osteoporotic fracture.

FROM A CLINICAL POINT OF VIEW, TBS IS ABLE:

- To predict future fracture risk \[14\-15\]
- In combination with BMD, to increase the number of patients with a well identified risk \[14\-18\]
- To improve the management of patients with secondary osteoporosis (in which bone quality has a greater impact than bone quantity) \[19\-21\]
- To follow the evolution of a patients’ trabecular bone texture over time
- To monitor the effects of anti-resorptive or anabolic treatment \[22\-26\]

\[11\] Winzenrieth R et al. JCD 2012
\[12\] Hans D et al. JCD 2011
\[14\] Hans D et al. JBMR 2011
\[15\] Boutroy et al. OI 2011
\[16\] Rabier B et al. Bone 2010
\[17\] Winzenrieth R et al. CTI 2010
\[18\] Del Rio L et al. OI 2012
\[19\] Braezen et al. JCD 2012
\[20\] Colson F et al. JBMR 2009
\[21\] Maury E et al. JBMR 2010
\[26\] McClung MR et al. ASBMR 2012
OSTEOPOROSIS TREATMENT

The usefulness of treatments/interventions in osteoporosis is mainly due to the reduction in fracture risk they induce. We can distinguish:

- **Primary prevention of BMD loss**, a natural phenomenon related to age, increased by menopause and leading to osteoporosis in elderly women, with preventative measures relating to diet and lifestyle. These aim to reduce age-related bone loss by acting on measures of healthy living including: nutrition with sufficient calcium intake (1000-1500 mg/day), appropriate and regular physical activity, more or less complete elimination of exogenous intoxications like tobacco and alcohol as well as drugs affecting bone metabolism (corticosteroids, anticonvulsants, thyroid hormones at high doses), and vitamin D (800-1000 IU/day) supplementation if levels are inadequate, and/or if sun exposure is reduced.

- **Secondary prevention consists primarily of treatment** of bone, even if the items discussed in the context of primary prevention remain valid, especially to avoid any new fracture. Therapeutic decisions are not based solely on a patient’s densitometric result, but also on the analysis of all fracture risk factors. Once the «diagnosis» of osteoporosis or osteopenia is made, several treatments are available to physicians, depending upon the patient’s degree of lost BMD and their risk factors. Treatments are designed to increase bone strength, restore bone mass, or prevent further loss. There are two broad categories of treatment, both having recognized anti-fracture effects [28, 29]:

  - **Bone resorption inhibitors** (known to primarily increase bone density and bone microarchitecture) (e.g., PTH).

  - **Bone formation stimulants** (known to increase both bone density and bone microarchitecture) (e.g., PTH).

HOW TO TAKE TBS INTO ACCOUNT WHEN TREATING PATIENTS?

Currently, the main steps of osteoporosis diagnosis include an assessment of fracture risk (information obtained by questionnaire and integrating clinical risk factors for fracture), the measurement of bone density at both primary anatomical sites, and the evaluation of bone turnover biological markers. TBS is part of this clinical context, completing and enhancing the bone assessment made by the BMD by adding the dimension of bone quality. A patient with reduced BMD and high TBS will have a lower risk of fracture than a patient with reduced BMD and low TBS.

With all these elements, the clinician may make a diagnosis and then decide on the implementation, or not, of a preventative or curative treatment. The integration of TBS into the overall protocol of patient care is discussed in the following tables.
### 2. Interpretation Tables for patient management with TBS

#### MENOPAUSAL WOMAN WITHOUT FRAGILITY FRACTURE

<table>
<thead>
<tr>
<th>BMD</th>
<th>TBS</th>
<th>GLOBAL DIAGNOSIS</th>
<th>FRACTURE RISK</th>
<th>TREATMENT</th>
<th>COMPLEMENTARY EXAMINATION</th>
<th>BMD / TBS MONITORING (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>normal TBS ≥ 1.350</td>
<td>normal following WHO guidelines</td>
<td>low</td>
<td>nothing</td>
<td>nothing</td>
<td>no follow-up without any new clinical event</td>
</tr>
<tr>
<td></td>
<td>partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>normal following WHO guidelines</td>
<td>low</td>
<td>Ca + Vit D if needed(3)</td>
<td>nothing</td>
<td>60 months follow-up exam or new exam with any new clinical event</td>
</tr>
<tr>
<td></td>
<td>degraded TBS ≤ 1.200</td>
<td>normal following WHO guidelines</td>
<td>moderate</td>
<td>Ca + Vit D if needed(3)</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers</td>
<td>24-36 months follow-up depending on FRF</td>
</tr>
<tr>
<td>OSTEOPENIA</td>
<td>normal TBS ≥ 1.350</td>
<td>osteopenia following WHO guidelines</td>
<td>low or moderate (if other FRF(2))</td>
<td>Ca + Vit D if needed(3)</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers</td>
<td>36-60 months follow-up depending on FRF</td>
</tr>
<tr>
<td></td>
<td>partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>osteopenia following WHO guidelines</td>
<td>moderate</td>
<td>Ca + Vit D if needed(3), anti-resorptive treatment (based on FRF(2))</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers</td>
<td>24-48 months follow-up depending on FRF and treatment</td>
</tr>
<tr>
<td></td>
<td>degraded TBS ≤ 1.200</td>
<td>osteopenia following WHO guidelines</td>
<td>moderate to medium (if other FRF(2))</td>
<td>Ca + Vit D if needed(3), anti-resorptive treatment (based on FRF(2))</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers and Vertebral Fracture Assessment by DXA or X-ray</td>
<td>24 months</td>
</tr>
<tr>
<td>OSTEOPOROSIS</td>
<td>normal TBS ≥ 1.350</td>
<td>osteoporosis following WHO guidelines</td>
<td>moderate to medium (if other FRF(2))</td>
<td>Ca + Vit D if needed(3), anti-resorptive treatment (based on FRF(2))</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers and Vertebral Fracture Assessment by DXA or X-ray</td>
<td>24-36 months follow-up depending on FRF and treatment</td>
</tr>
<tr>
<td></td>
<td>partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>osteoporosis following WHO guidelines</td>
<td>moderate to medium (if other FRF(2))</td>
<td>Ca + Vit D if needed(3), anti-resorptive treatment</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or X-ray</td>
<td>24-36 months follow-up depending on FRF and treatment</td>
</tr>
<tr>
<td></td>
<td>degraded TBS ≤ 1.200</td>
<td>osteoporosis following WHO guidelines</td>
<td>medium to high (if other FRF(2))</td>
<td>Ca + Vit D if needed(3), anti-resorptive or anabolic treatment (if fragility fracture discovery)</td>
<td>phosphocalcic chemistry test, bone turnover biomarkers and Vertebral Fracture Assessment by DXA or X-ray</td>
<td>24 months</td>
</tr>
</tbody>
</table>

**NOTE:** Depending on the therapeutic agent, the influence on bone microarchitecture would be different

1. Based on nutrition questionnaire and 25 OHD measurement
2. Fracture risk factors (FRF) include clinical risk factors, VFA outcome as well as bone remodeling biomarkers
3. Depending on countries, a BMD/TBS test is advised only at the end of the treatment cycle, so 4-5 years (except particular situation or issue)
# Menopausal Woman with a Vertebreal Fragility Fracture Grade 2 or 3 or a Non Vertebral Major\(^{(1)}\) OP Fracture

<table>
<thead>
<tr>
<th>BMD / TBS Monitoring(^{(3)})</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMAL</strong></td>
<td></td>
</tr>
<tr>
<td>Normal TBS ≥ 1.350</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td>Partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td>Degraded TBS ≤ 1.200</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td><strong>OSTEOPENIA</strong></td>
<td></td>
</tr>
<tr>
<td>Normal TBS ≥ 1.350</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td>Partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td>Degraded TBS ≤ 1.200</td>
<td>clinical osteoporosis</td>
</tr>
<tr>
<td><strong>OSTEOPOROSIS</strong></td>
<td></td>
</tr>
<tr>
<td>Normal TBS ≥ 1.350</td>
<td>severe osteoporosis based on WHO guidelines</td>
</tr>
<tr>
<td>Partially degraded 1.200 &lt; TBS &lt; 1.350</td>
<td>severe osteoporosis based on WHO guidelines</td>
</tr>
<tr>
<td>Degraded TBS ≤ 1.200</td>
<td>severe osteoporosis based on WHO guidelines</td>
</tr>
</tbody>
</table>

**NOTE-1:** Corticosteroids will influence the global clinical assessment. **NOTE-2:** Depending on the therapeutic agent, the influence on bone microarchitecture would be different. (1) Major fragility fractures: upper femur fractures, humerus fractures, wrist fractures and clinical vertebral fractures (different from a symptomatic or symptomatic X-ray vertebral fractures). In some countries lower femur, upper tibial, 3 ribs or more, pelvic fractures are also considered major fractures as well. (2) Based on nutrition questionnaire and 25 OH D measurement. (3) Fracture risk factors (FRF) include clinical risk factors, VFA outcome as well as bone remodeling biomarkers. (4) Depending on countries, a BMD/TBS test is advised only at the end of the treatment cycle, so 4-5 years (except particular situation or issue).
### Monitoring

<table>
<thead>
<tr>
<th>BMD L1-4 or Femur</th>
<th>L1-4 TBS</th>
<th>Comments / Interpretation</th>
</tr>
</thead>
</table>
| ↑                 | ↑       | Unexpected positive trend with significant BMD and TBS increases  
→ Fracture risk reduction  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• No changes in patient care management |
| ↑                 | ↓       | Unexpected significant BMD increase and expected TBS decrease  
→ Stable fracture risk  
• Check biological and clinical risk factors for fracture  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• No changes in patient care management |
| ↑                 | →       | Unexpected stable to positive evolution of BMD and TBS  
→ Slight reduction of fracture risk  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• No changes in patient care management |
| ↓                 | ↑       | Expected decrease in BMD and unexpected significant TBS increase  
→ Stable fracture risk  
• Check biological and clinical risk factors for fracture  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ↓                 | ↓       | Expected significant BMD and TBS decreases  
→ Increase of fracture risk  
• Check biological and clinical risk factors for fracture  
• Treatment to be evaluated based on CRF, BMD and TBS values (see previous tables)  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ↓                 | →       | Significant and expected BMD decrease, stable TBS  
→ Slight increase of fracture risk  
• Check biological and clinical risk factors for fracture  
• Treatment to be evaluated based on CRF, BMD and TBS values (see previous tables)  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| →                 | ↑       | Unexpected positive to stable evolution of BMD and TBS  
→ Slight reduction of fracture risk  
• Check biological and clinical risk factors for fracture  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• No changes in patient care management |
| ↓                 | ↓       | Stable BMD and expected decrease in TBS  
→ Slight increase of fracture risk  
• Check biological and clinical risk factors for fracture  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• Treatment to be evaluated based on CRF, BMD and TBS values (see previous tables) |
| ↓                 | →       | Stable BMD and TBS, expected or not according to the age of the patient  
→ Stable fracture risk  
• Look for possible artifacts – check bone area selection consistency between one examination to another  
• No changes in patient care management |

### BMD AND TBS EVOLUTION (ABOVE LSC) FOR MENOPAUSAL WOMAN WITH OP TREATMENT 1/2

<table>
<thead>
<tr>
<th>BMD L1-4 OR FEMUR</th>
<th>L1-4 TBS</th>
<th>COMMENTS / INTERPRETATION</th>
</tr>
</thead>
</table>
| ✓                 | ✓        | • Without any new fracture, global microarchitectural improvement and increase of BMD (standard effect of anabolic treatment and of some anti-resorptive treatment), demonstrating treatment compliance and efficacy  
• No change in patient care management  
• Follow-up exam in 24 months, depending on treatment duration or intended pause | **Reduction of fracture risk** |
| ✓                 | ✗        | • BMD increase and microarchitectural deterioration  
- check treatment compliance  
- check for new fracture(s)  
- check bone area selection consistency between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Depending on BMD and TBS values, follow-up exam in 24 months | **Stable fracture risk** |
| ✓                 | ✓        | • BMD increase and stable microarchitecture (standard effect of anti-resorptive treatment)  
- check treatment compliance  
- check for new fracture(s)  
- check bone area selection consistency between one examination to another  
• No changes in patient care management  
• Depending on BMD and TBS values, follow-up exam in 24 months | **Slight reduction of fracture risk** |
| ✓                 | ✗        | • BMD loss, microarchitectural improvement  
- check treatment compliance  
- check for new fracture(s)  
- check bone area selection consistency between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Follow-up exam in 24 months | **Stable fracture risk** |
| ✗                 | ✓        | • Deterioration of both BMD and microarchitectural  
- check treatment compliance  
- check for new fracture(s)  
- check bone area selection consistency between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Depending on BMD and TBS values, follow-up exam in 24 months | **Increase fracture risk** |
## BMD AND TBS EVOLUTION (ABOVE LSC) FOR MENOPAUSAL WOMAN WITH OP TREATMENT 2/2

<table>
<thead>
<tr>
<th>BMD L1-4 OR FEMUR</th>
<th>L1-4 TBS</th>
<th>COMMENTS / INTERPRETATION</th>
</tr>
</thead>
</table>
| ![down arrow]     | ![down arrow] | • BMD decrease and stable microarchitecture  
  - check treatment compliance  
  - check for new fracture(s)  
  - check bone area selection consistancy between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ![up arrow]       | ![down arrow] | ![Slight increase of fracture risk] |
| ![down arrow]     | ![up arrow]   | • Stable BMD and microarchitectural improvement  
  - check treatment compliance  
  - check for new fracture(s)  
  - check bone area selection consistancy between one examination to another  
• No changes in patient care management  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ![down arrow]     | ![down arrow] | ![Slight reduction of fracture risk] |
| ![up arrow]       | ![up arrow]   | • Stable BMD and microarchitectural deterioration  
  - check treatment compliance  
  - check for new fracture(s)  
  - check bone area selection consistancy between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ![down arrow]     | ![up arrow]   | ![Slight increase of fracture risk] |
| ![down arrow]     | ![up arrow]   | • Stable BMD and microarchitecture  
  - check treatment compliance  
  - check for new fracture(s)  
  - check bone area selection consistancy between one examination to another  
• Check biological\(^1\) and clinical risk factors (CRF) for fracture  
• Incomplete efficacy of current treatment; consider new treatment\(^2\)  
• Depending on BMD and TBS values, follow-up exam in 24 months |
| ![up arrow]       | ![up arrow]   | ![Stable fracture risk] |


\(^2\) Switch from an oral anti-resorptive treatment to an injectable preparation; or, if the patient's FRF allows, from an anti-resorptive to anabolic drug
3. Clinical cases combining both BMD and TBS

**CASE #1**

**POSTMENOPAUSAL OSTEOSPOROSIS**

**HISTORY:**
- 63 year-old woman
- No history of fracture
- Menopause at age 50
- HRT for 2 years
- Osteoporotic mother
- No smoking
- Alcohol consumption: 1.5dl of wine/day
- Regular physical activity
- Normal weight
- Daily calcium intake: 500 to 1000 mg
- History of leukemia in remission, treated with Glivec®

**CLINICAL ASSESSMENT:**
Densitometric osteoporosis diagnosed 6 years ago. Introduction of Calcimagon® D3 500/400 1x/day (~Calcium carbonate) long-term and alendronate 70 mg once weekly for one year.

**BONE ASSESSMENT:**
Spine BMD T-score: -2.8 SD, Total Hip BMD T-score: -1.4 SD and Femoral Neck BMD T-score: -2.0 SD. Compared to the previous examination (5 years ago), significant losses, including 6% in the spine; stable results in the femur. No vertebral fractures identified on VFA. TBS: 1.357.

**BIOLOGICAL ASSESSMENT:**
Cross-linked C-telopeptide (CTX) 365 ng/l (target < 573), 25-OH vitamin D 31.5 µg/l (target > 30). Phosphocalcic chemistry panel demonstrating normal renal and thyroid functions.

**MEDICAL DECISION:**
In view of healthy living habits, low CTX and normal TBS values, we have decided not to prescribe any anti-resorptive agents, despite densitometric osteoporosis.

**MONITORING:**
CTX and 25-OH vitamin D to be reassessed in one year. DXA, VFA, TBS and CTX in 2 years.

**CASE #2**

**ANTI-AROMATASE TREATMENT AND BONE**

**HISTORY:**
- 62 year-old woman
- Menopause at the age of 46
- No hormone replacement therapy
- Height: 159 cm; weight: 73 kg; BMI = 28.87 kg/m²
- Breast cancer in 2010, treated with surgery, radiotherapy and anti-aromatase.

**INITIAL BONE ASSESSMENT AND MONITORING:**
- Spine and femoral osteopenia in 2010.
- Follow-up visit in 2012 (relative to 2010): significant bone loss, in the spine of -4.7% and in the hip of -3.7%. No fractures by VFA - Aggravation of BMD leading to femoral osteoporosis.

**CLINICAL ASSESSMENT:**
No vertebral fracture. No tobacco. Normal alcohol consumption. Dietary calcium intake between 500 and 1000 mg/day. Mother history of hip fracture. FRAX value of 11.1% for major osteoporotic fracture.

**BMD:**
- Spine and femoral osteopenia in 2010.
- Follow-up visit in 2012 (relative to 2010): significant bone loss, in the spine of -4.7% and in the hip of -3.7%. No fractures by VFA - Aggravation of BMD leading to femoral osteoporosis.

**MEDICAL DECISION:**
Given the significant losses in BMD and TBS, a specific anti-resorptive treatment is indicated. Depending on the country, the choice will be either Aclasta® or Prolia®. If we can choose between these two drugs, we would select Prolia® (denosumab) which has demonstrated a greater impact on microarchitecture.

**MONITORING:**
Biomarkers in 3 months to evaluate the efficacy of treatment. DXA and TBS in 12 to 24 months.

**NOTE:** with an anti-aromatase drug, there is often a larger decrease in TBS than BMD.

It is recommended to express discrepancies between two examination results in absolute values, rather than as percentages. However, we have elected to express both values as percentages in this document, in order to ease the lecture and comprehension of the clinical cases.
HIV AND BONE

**HISTORY:**
- 66 year-old woman with stage A2 HIV infection diagnosed 15 years ago, treated with several anti-retroviral drugs
- Hepatic steatosis and metabolic syndrome
- At risk for alcohol use
- History of hyperthyroidism from Graves’ disease
- Weight: 75.5 kg; height: 160 cm; BMI: 29.49 kg/m$^2$

**CLINICAL ASSESSMENT:**
Osteoporosis with wrist fracture 12 years ago. Alendronate 70 mg/week for 3 years then quarterly intravenous ibandronate for 2 years, totalling 5 years of bisphosphonates between 2004 and 2009. Has taken vitamin D and supplemental calcium for more than 8 years.

**BONE ASSESSMENT:**
Spine BMD T-score -2.2 SD, Total Hip BMD T-score -1.9 SD, and Femoral Neck BMD T-score -2.0 SD. No vertebral fractures on VFA. TBS: 0.954.

**BIOLOGICAL ASSESSMENT:**
CTX 163 ng/l (target < 573), 25-OH vitamin D 36.2 µg/l (target > 30).

**MEDICAL DECISION:**
The increase in bone mineral density was reassuring, but the discovery of an unexpected vertebral fracture after two years of treatment left us confused about this case. The patient’s weight was stable between 2004 and 2011. It was decided to retrospectively analyse TBS values corresponding to the three DXA examinations the patient had had.

**RETROSPECTIVE BONE ASSESSMENT:**
- Retrospective analysis 2004: TBS = 1.290 (partial architectural degradation)
- Retrospective analysis 2008: 1.135 (degraded): significant loss of -12% (beyond LSC)
- Retrospective analysis 2011: TBS = 1.031 (highly degraded): additional significant loss of -9.2% (beyond LSC)

**REVIEWED MEDICAL DECISION:**
In view of the alarming TBS results and the vertebral fracture in late 2010, despite the increase in BMD, we reconsidered our therapeutic decision to use an anabolic. A preliminary request was sent to the insurance company and, after validation, we placed the patient on teriparatide.

**MONITORING:**
Biological markers in 3 months to verify treatment compliance. DXA and TBS in 24 months.

Follow-up of Corticosteroid-Induced Osteoporosis

**CASE #3**

**HISTORY:**
- 66 year-old woman with stage A2 HIV infection diagnosed 15 years ago, treated with several anti-retroviral drugs
- Hepatic steatosis and metabolic syndrome
- At risk for alcohol use
- History of hyperthyroidism from Graves’ disease
- Weight: 75.5 kg; height: 160 cm; BMI: 29.49 kg/m$^2$

**CLINICAL ASSESSMENT:**
Osteoporosis with wrist fracture 12 years ago. Alendronate 70 mg/week for 3 years then quarterly intravenous ibandronate for 2 years, totalling 5 years of bisphosphonates between 2004 and 2009. Has taken vitamin D and supplemental calcium for more than 8 years.

**BONE ASSESSMENT:**
Spine BMD T-score -2.2 SD, Total Hip BMD T-score -1.9 SD, and Femoral Neck BMD T-score -2.0 SD. No vertebral fractures on VFA. TBS: 0.954.

**BIOLOGICAL ASSESSMENT:**
CTX 163 ng/l (target < 573), 25-OH vitamin D 36.2 µg/l (target > 30).

**MEDICAL DECISION:**
Due to the duration of exposure to bisphosphonates and partial inhibition of CTX reflecting the residual activity of bisphosphonates, no new therapy has been provided. The strong degradation of TBS may be related to HIV infection and, perhaps, to anti-retroviral treatment. However, if a decision is made to restart therapy, teriparatide should be discussed.

**MONITORING:**
DXA and TBS in 24 months to evaluate the potential initiation of teriparatide.

**CASE #4**

**HISTORY:**
- 64 year-old woman
- Menopause at age 51
- Fractures at D10 and D12
- Height: 165 cm; weight: 71.7kg; BMI: 26.3kg/m$^2$
- Polymyalgia rheumatica (PR) diagnosed 10 years ago, and has been on 7.5 to 10 mg/day prednisone ever since
- No monitoring or preventive treatment initiated in 2004 for corticosteroid-induced osteoporosis at her first visit for DXA examination (normal exam), apart from a daily vitamin and calcium supplementation.

**CLINICAL ASSESSMENT:**
No family history of osteoporosis. No smoking. Normal alcohol consumption. Calcium intake between 500 and 1000 mg/day. Polyarteritis Nodosa (PAN) diagnosed.

**INITIAL AND FOLLOW-UP BONE ASSESSMENT:**
1st examination in 2004: bone mineral density normal at the spine and hip, and no fractures detected on VFA.

Follow-up visit in 2008: significant bone loss at the spine: -14.1% (beyond LSC), with -5.3% bone loss at the hip. No fracture by VFA

Initiation of treatment with alendronate 70 mg/week.

Follow-up visit in 2011: significant gain at the spine of +9.0% (beyond LSC), with +3.3% gain at the hip; but a fracture is detected by VFA at D11 (consistent with an acute episode of back pain at the end of 2010, precipitated by minor physical effort).

**REVIEWED MEDICAL DECISION:**
In view of the alarming TBS results and the vertebral fracture in late 2010, despite the increase in BMD, we reconsidered our therapeutic decision to use an anabolic. A preliminary request was sent to the insurance company and, after validation, we placed the patient on teriparatide.

**MONITORING:**
Biological markers in 3 months to verify treatment compliance. DXA and TBS in 24 months.
**HISTORY:**
- 59 year-old woman
- No history of fracture
- Menopause at age 50
- Smoking habit
- Regular physical activity
- Normal weight
- Daily calcium intake: 500 to 1000 mg.

**CLINICAL ASSESSMENT:**
Densitometric osteoporosis diagnosed in the context of a clinical trial.

**BONE ASSESSMENT:**
Spine BMD T-score -3.5 SD (no significant discrepancies between vertebrae), Total Hip BMD T-score -1.8 SD and Femoral Neck BMD T-score -1.9 SD. No vertebral fracture identified on VFA. TBS: 1.242.

**BIOLOGICAL ASSESSMENT:**
CTX 803 ng/l (target < 573); 25-OH vitamin D 22 µg/l (target > 30). Phosphocalcic test demonstrating normal renal and thyroid functions.

**MEDICAL DECISION:**
In view of the very low T-score in the spine and the high CTX, we have decided to prescribe an anti-resorptive drug, despite the patient’s young age and the absence of fractures. Plus, in view of partially degraded TBS, we chose to give either Prolia® (denosumab) or Protelos® (strontium ranelate) (in accordance with local health society reimbursement rules) as they are known for their positive influence on bone microarchitectural reconstruction, relative to bisphosphonates. We strongly suggest that our patient quit smoking and introduce Calcimagon® D3 500/400 once daily long-term.

**MONITORING:**
CTX to be checked in 3 months. CTX and 25-OH vitamin D in one year. DXA, VFA, TBS and CTX in two years.

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**HISTORY:**
- 62 year-old woman
- 1st DXA in February 2011 because of back pain.
- We discovered a family history of osteoporosis while reviewing clinical risk factors
- The patient is taking vitamin D and a calcium supplement.

**CLINICAL ASSESSMENT:**
No fracture. Physiological menopause; no other clinical risk factors for fracture.

**1ST BONE ASSESSMENT:**
Spine BMD T-score -1.8 SD (no degenerative disorders), Total Hip BMD T-score -1.8 SD and Femoral Neck BMD T-score -1.4 SD. No vertebral fractures on VFA.

**MEDICAL DECISION:**
In view of the BMD values, no specific treatment was initiated beyond vitamin and calcium supplementation.

**MONITORING:**
DXA, VFA and TBS in 24 months.

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**SEPTEMBER 2012:**
We were informed by the patient that she recently had fractures at L2 and L3, in the absence of trauma. Fractures were confirmed by a radiologist. Retrospective analysis of her 2011 DXA scan and TBS calculation: TBS L1-L4 (excluding L2-3) results: 1.129 (highly degraded).

**REVIEWED MEDICAL DECISION:**
In view of the concerning TBS result and the two unexpected vertebral fractures in 2012, it was decided to change her treatment regimen, despite her only being osteopenic, proposing Protelos® (strontium ranelate) or Prolia® (denosumab) (depending on Social Health Agency conditions for reimbursement), both known for their superior positive impact on bone microarchitecture relative to bisphosphonates. If TBS values had been moderate (above 1.200), a bisphosphonate would have been given by first intention. Ongoing biological examination will help us to make our final decision.

**MONITORING:**
DXA scan
OSTEONEGENESIS IMPERFECTA

HISTORY:
- 55 year-old man diagnosed with type IV osteogenesis imperfecta several years ago
- Sustained 40 fractures and had frequent surgery throughout childhood and adolescence
- No more fractures then until the age of 46, when he fractured his scapula
- At the age of 53, he had a traumatic bifocal fracture of the left humerus and a right subtrochanteric insufficiency fracture.

CLINICAL ASSESSMENT:
The patient has no other risk factors for osteoporosis, beyond functional limitations linked to the aftermath of his past fractures. He lives a healthy lifestyle. He is 174 cm tall and weights 85.7kg; BMI = 28.14 kg/m². His BMD values have been stable over the past few years.

BONE ASSESSMENT:
Spine BMD T-score -3.1 SD, Total Hip BMD T-score +1.4 SD and Femoral Neck BMD T-score +0.5 SD (Spine T-score probably overestimated because of degenerative changes. Hip T-score also may be falsely high secondary to sequelae of a subperiosteal hematoma). TBS: 1.085.

MEDICAL DECISION:
This case illustrates both the difficulty in interpreting a DXA with artifacts and the strong discrepancy between BMD and TBS in cases of osteogenesis imperfecta. Unfortunately, despite regular monitoring and repeated encouragement as to the need to initiate some sort of treatment, the patient has repeatedly refused. Given the history of fractures and the strongly degraded TBS, teriparatide would be our treatment of choice, though few studies have reported on the use of PTH in patients with osteogenesis imperfecta.

MONITORING:
Follow-up of treatment compliance and efficacy via P1NP markers after three months. DXA + TBS at 24 months.

NOTE:
With a low T-score and normal TBS, an anti-resorptive drug would have been prescribed as a first intention treatment because of prescription and reimbursement rules in the country. This case emphasizes how smoking and early menopause can both have a major negative impact on bone microarchitecture.

VITAMIN D DEFICIENCY AND VERTEBRAL FRACTURE

HISTORY:
- 67 year-old woman with normal BMI
- Menopause at the age of 53
- History of traumatic vertebral fracture at D12 (in 2010) confirmed by radiography. Recurrent rachialgia from neck to sacrum deemed secondary to degenerative changes
- Routine monitoring visit.

CLINICAL ASSESSMENT:
Maternal family history of osteoporosis. No smoking and normal alcohol intake. Calcium intake between 500 and 1000 mg/day. No other clinical risk factors. Back pain is considered consistent with her medical profile.

BONE ASSESSMENT:
Spine BMD T-score -1.3 SD (degenerative changes but no significant discrepancy between each independent vertebrae), Total Hip BMD T-score -1.2 SD, and Femoral Neck BMD T-score -1.1 SD. TBS: 1.140.

BIOLOGICAL ASSESSMENT:
Hypovitaminosis D with 25 OH D2 D3 < 4 ng/l. Ca, P, and PTH normal. VS 10. NF normal.

MEDICAL DECISION:
Given TBS results that show an unexpectedly high level of bone degradation, we decided to undertake additional radiological evaluation. Radiographs reveal a «new» vertebral fracture at L4. This leads to prescription of a lumbar belt, increased analgesic doses, appropriate supplementation with vitamin D and calcium, and initiation of a bisphosphonate.

MONITORING:
DXA and TBS in 24 months.

NOTE:
TBS provides validity to the diagnosis of fragility fracture despite only mild osteopaenia per densitometry.

EARLY MENOPAUSE AND VERTEBRAL FRACTURE

HISTORY:
- 55 year-old man diagnosed with type IV osteogenesis imperfecta several years ago
- Sustained 40 fractures and had frequent surgery throughout childhood and adolescence
- No more fractures then until the age of 46, when he fractured his scapula
- At the age of 53, he had a traumatic bifocal fracture of the left humerus and a right subtrochanteric insufficiency fracture.

CLINICAL ASSESSMENT:
The patient has no other risk factors for osteoporosis, beyond functional limitations linked to the aftermath of his past fractures. He lives a healthy lifestyle. He is 174 cm tall and weights 85.7kg; BMI = 28.14 kg/m². His BMD values have been stable over the past few years.

BONE ASSESSMENT:
Spine BMD T-score -3.1 SD, Total Hip BMD T-score +1.4 SD and Femoral Neck BMD T-score +0.5 SD (Spine T-score probably overestimated because of degenerative changes. Hip T-score also may be falsely high secondary to sequelae of a subperiosteal hematoma). TBS: 1.085.

MEDICAL DECISION:
This case illustrates both the difficulty in interpreting a DXA with artifacts and the strong discrepancy between BMD and TBS in cases of osteogenesis imperfecta. Unfortunately, despite regular monitoring and repeated encouragement as to the need to initiate some sort of treatment, the patient has repeatedly refused. Given the history of fractures and the strongly degraded TBS, teriparatide would be our treatment of choice, though few studies have reported on the use of PTH in patients with osteogenesis imperfecta.

MONITORING:
Follow-up of treatment compliance and efficacy via P1NP markers after three months. DXA + TBS at 24 months.

NOTE:
With a low T-score and normal TBS, an anti-resorptive drug would have been prescribed as a first intention treatment because of prescription and reimbursement rules in the country. This case emphasizes how smoking and early menopause can both have a major negative impact on bone microarchitecture.
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