Editorial

Dear colleagues,

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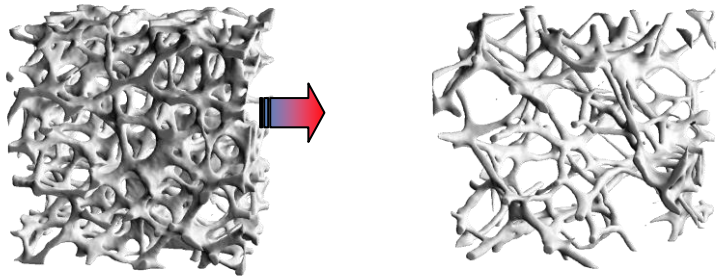
PS: The cases presented in Part 3 of this document are inspired by real clinical cases but have been adapted to ensure confidentiality. It is important to note that clinical cases reflect individual practices and do not necessarily reflect official guidelines in force (repayment of drugs, etc ...) which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



normal osteoporotic

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 [1].

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 [2]. 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 [3], 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 [4]. 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.

__[1]__ WHO Study Group (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser. __[2]__ NIH Consensus Development Panel on Osteoporosis Prevention Diagnosis and Therapy (2001) Osteoporosis prevention, diagnosis, and therapy. JAMA 285:785-795. __[[3]__ Rice JC et al. J Biomech 1988 __[4]__ Cooper C et al. OI 1992.

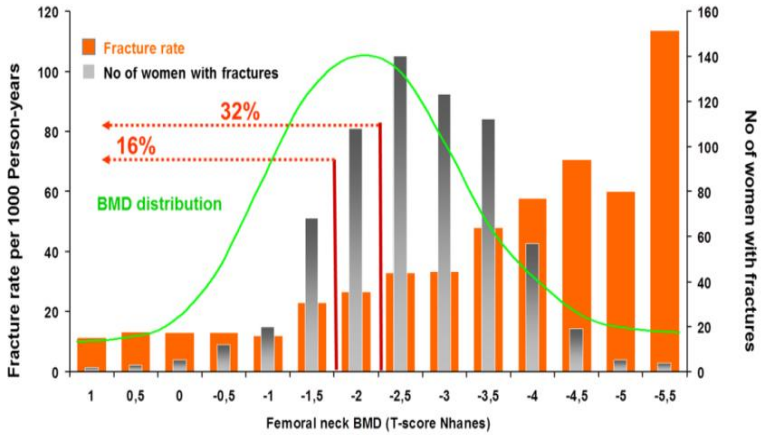
Bone imaging in routine clinical practice

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/cm^2). 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 [6-7].
[6] LD Hordon et al. Bone 2000 [7] McClung MR Bone 2006.

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 [8]. These markers are measured in serum, plasma and urine [8]. 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.

[8] *Naylor K, Eastell R. 2012 Nat Rev Rheumatol.*

Clinical risk factors for fractures

Besides BMD, several clinical factors associated with osteoporotic fractures have been identified in numerous epidemiological studies [9]. These osteoporotic fracture risk factors are, in some cases, reversible with or without treatment, measurable, and independent of BMD. The best known are [9]: age, female sex, a fragility fracture (caused by minimal trauma) occurring after 50 years of age, family history of a first degree osteoporotic fracture, long-term intake of corticosteroids, early menopause, alcoholism, smoking, BMI less than 19kg/m² and diseases such as rheumatoid arthritis, type I diabetes and hyperparathyroidism. **These clinical risk factors are commonly used** by clinicians **and combined with data from BMD** and/or turnover biomarkers for the diagnosis, monitoring and treatment of their patients. To facilitate the combination of these clinical and radiological data, **the FRAX® has recently been developed [10]**: 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-

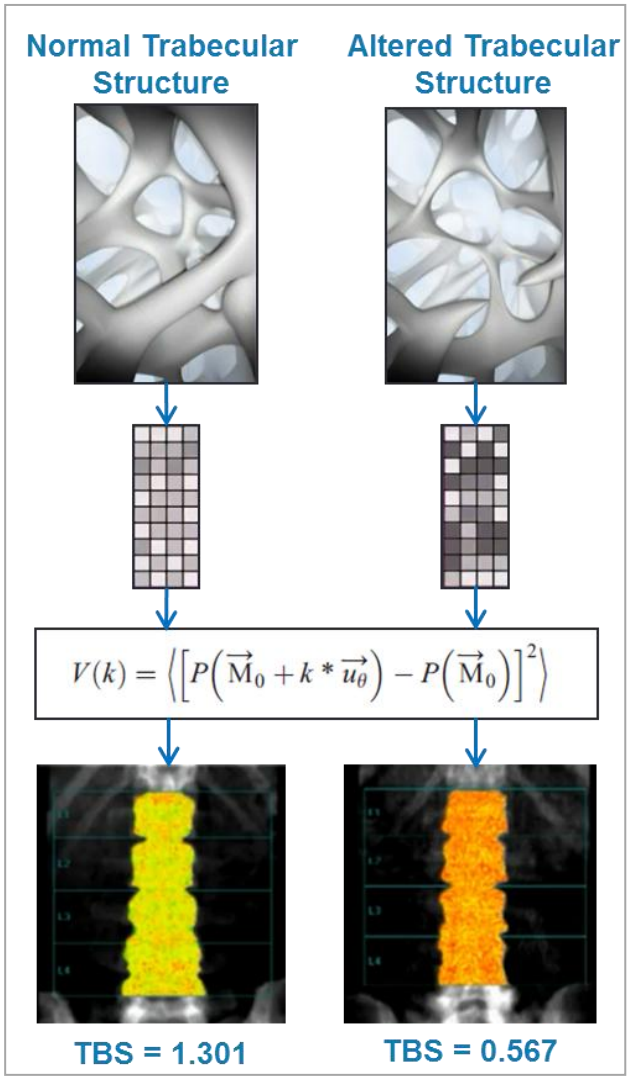
making thresholds have been defined to determine treatment, which also differ from one country to another. Moreover, the FRAX® provides no guidance as to the type of treatment that should be prescribed.

[9] Kanis JA, on behalf of the World Health Organisation Scientific Group. Assessment of osteoporosis at the primary health care level. WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield 2007. ***[10]*** *J.A. Kanis et al. OI 2008*

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 [11] 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".

[11] Seeman E, Delmas PD N Engl J Med 2006



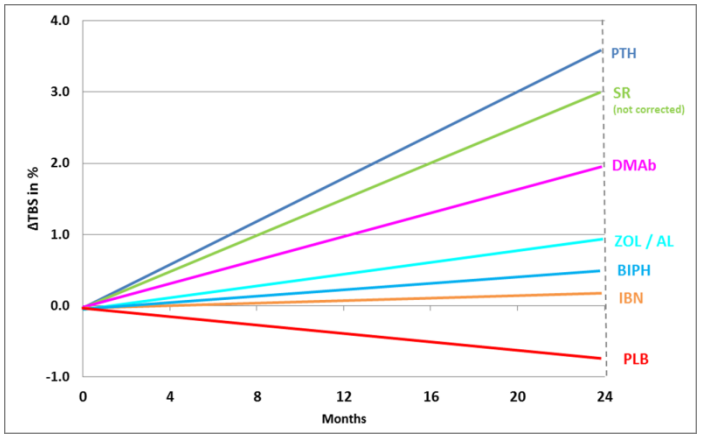
TBS (Trabecular Bone Score) is a texture parameter that can be computed from DXA images, and that quantifies local variations in pixels intensities. TBS is derived from the experimental variogram obtained from the gray levels of a DXA image.

It has been shown that **TBS is related to the structural condition of bone microarchitecture** [12-14]. 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 [12-13] and with the SMI index ("structure model index"). [14] 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.

[12] Winzenrieth R.et al. JCD 2012 [13] Hans D et al.JCD 2011 [14] Roux JP. Et al Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P597

From a clinical point of view, TBS is able:

- To **predict future fracture risk** [15,16]
- In combination with BMD, to **increase the number of patients with a well identified risk** [15-19]
- To **improve the management of patients** with secondary osteoporosis (in which bone quality has a greater impact than bone quantity) [20-22]
- To **follow the evolution of a patients' trabecular bone texture** over time
- To **monitor the effects of anti-resorptive or anabolic treatment** [23-27]

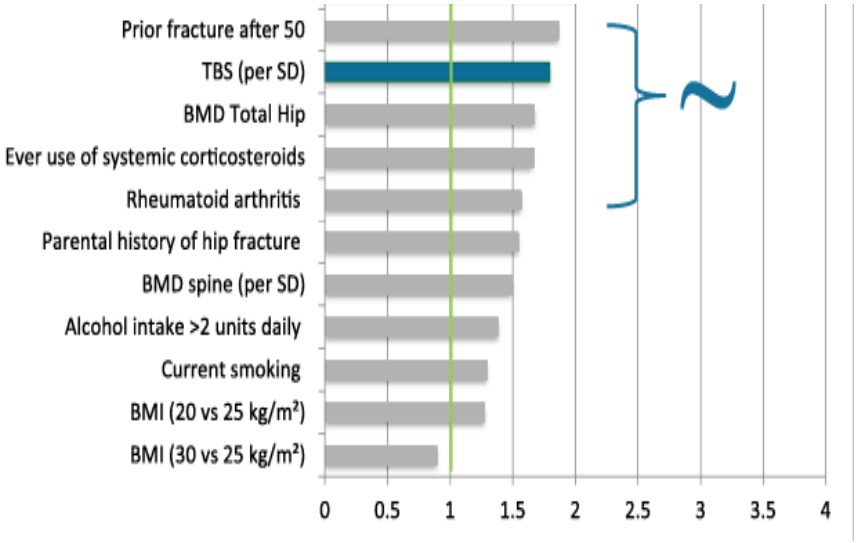


Summary of studies relating to the effect of treatments on TBS normalized to 24 months. Attention these studies are not directly comparable with each other

[15] Hans D, et al. JBMR 2011. [16] Boutroy et al.OI 2011I. [17] Rabier B et al. Bone 2010 [18] Winzenrieth R et al.CTI 2010 [19] Del Rio L et al .OI 2012 [20] Breban et al. JCD 2012 [21] Colson F et al. JBMR 2009 [22] Maury E et al. JBMR 2010 [23] Hans D. et al Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P471, [24] Popp et al. Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P599,[25] Gunther et al. Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P609,[26] Hadji et al. Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P518.[27] McClung MR et al. ASBMR 2012.

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 [28]. TBS can therefore be used as a risk factor for osteoporotic fracture.

[28] Hans et al. Osteoporosis Int 2012. 23: (Suppl 2): S85-386; P542



Relative Risk of TBS and BMD at the spine and total hip expressed by standard deviation and compared with relative risks of major fracture clinical risk factors included in FRAX®.

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 [29, 30]:

- **Bone resorption inhibitors** (known to primarily increase bone density and, depending on the drug, maintain bone microarchitecture (e.g., bisphosphonates) and
- **Bone formation stimulants** (known to increase both bone density and bone microarchitecture) (e.g., PTH).

[29] Silverman S. et al. OI 2012. [30] Chen JS. et al. Nat Rev Endocrinol. 2011

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.

Summary tables of examples of patient management:

Prerequisites for using TBS

- Best practices, as defined by your national societies and especially the ISCD, must be observed when DXA is acquired
- TBS values are guaranteed for Body Mass Index (BMI) ranging from 15 to 35 kg/m² ~~(BMI is considered here as a substitute for soft tissue thickness)~~
- The WHO classification scheme for densitometric osteoporosis does not apply to TBS
- No TBS curve for normality is available for men
- TBS measures should not be interpreted in cases of significant scoliosis
- Clinical judgment remains paramount in the management of patients
- The "Least Significant Change" (LSC) can also be known as the "Smallest Significant Change" (SSC) or "Smallest Significant Value" (SSV). This is calculated for TBS in the same way as for BMD. For TBS, it is in the range of 3-5%, depending on the studies.

Menopausal woman (without fragility fracture)

BMD	TBS	Global diagnostic	Fracture risk	Treatment	Complementory exams	BMD / TBS monitoring °
Normal	**normal TBS ≥ 1.350**	Normal following WHO guidelines	low	nothing	nothing	no follow up without any new clinical event
	partially degraded 1.200 < TBS < 1.350	Normal following WHO guidelines	low	Ca + Vit D if needed*	nothing	60 months follow up exam or new exam with any new clinical event
	degraded TBS ≤ 1.200	Normal following WHO guidelines	moderate	Ca + Vit D if needed*	phosphocalcic chemistry test, bone turnover biomarkers	24-36 months follow up depending on FRF
Osteopénia	**normal TBS ≥ 1.350**	Osteopenia following WHO guidelines	low or moderate (if other Fracture Risk Factors- FRF)	Ca + Vit D if needed*	phosphocalcic chemistry test, bone turnover biomarkers	36 à 60 months follow up depending on FRF
	partially degraded 1.200 < TBS < 1.350	Osteopenia following WHO guidelines	moderate	Ca + Vit D if needed* , anti resorptive treatment (based on FRF)	phosphocalcic chemistry test, bone turnover biomarkers	24-48 months follow up depending on FRF and treatment
	degraded TBS ≤ 1.200	Osteopenia following WHO guidelines	moderate to medium (if other FRF)	Ca + Vit D if needed* , anti resorptive treatment (based on FRF)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral Fracture Assessment by DXA or Xray	24 months
Osteoporosis	**normal TBS ≥ 1.350**	Osteoporosis following WHO guidelines	moderate to medium (if other FRF)	Ca + Vit D if needed* , anti resorptive treatment (based on FRF)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24-36 months follow up depending on FRF and treatment
	partially degraded 1.200 < TBS < 1.350	Osteoporosis following WHO guidelines	moderate to medium (if other FRF)	Ca + Vit D if needed* , anti resorptive treatment (based on FRF)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24-36 months follow up depending on FRF and treatment
	degraded TBS ≤ 1.200	Osteoporosis following WHO guidelines	medium to high (if other FRF)	Ca + Vit D if needed* , anti resorptive or anabolic treatment (if fragility fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months

* based on nutrition questionnaire and 25 OH D measurement

fracture risk factors (FRF) include clinical risk factors, BMD and TBS as well as bone remodeling biomarkers

° depending on countries, a BMD/TBS test is adviced only at the end of the treatment cycle , so 4-5years (except particular situation or issue)

Menopaused woman (with ≥ 1 fragility vertebral fracture grade 2 or 3 OR ≥ 1 non vertebral major OP fracture)

BMD	TBS	Global diagnostic	Fracture risk	Treatment	Complementory exams	BMD / TBS monitoring °
Normal	normal TBS ≥ 1.350	Clinical Osteoporosis	moderate	Ca + Vit D if needed*, anti resorptive treatment (based on type and risk factor of the fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	partially degraded 1.200 < TBS < 1.350	Clinical Osteoporosis	medium	Ca + Vit D if needed*, anti resorptive treatment (based on type and risk factor of the fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	degraded TBS ≤ 1.200	Clinical Osteoporosis	medium or high (if other FRF)	Ca + Vit D if needed*, anti resorptive treatment (based on type and risk factor of the fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
Osteopénia	normal TBS ≥ 1.350	Clinical Osteoporosis	medium	Ca + Vit D if needed*, anti resorptive treatment (based on type and risk factor of the fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	partially degraded 1.200 < TBS < 1.350	Clinical Osteoporosis	medium or high (if other FRF)	Ca + Vit D if needed*, anti resorptive treatment (based on type and risk factor of the fracture)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	degraded TBS ≤ 1.200	Clinical Osteoporosis	High or very high (if other FRF)	Ca + Vit D if needed*, anti resorptive or anabolic treatment (based on type and number of fracture),	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
Osteoporosis	normal TBS ≥ 1.350	severe osteoporosis based on WHO guidelines	high	Ca + Vit D if needed*, anti resorptive treatment (if several fractures AND a BMD Tscore < -3.5)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	partially degraded 1.200 < TBS < 1.350	severe osteoporosis based on WHO guidelines	haut ou très haut (si présence d'autres FDR de la fracture)	Ca + Vit D if needed*, anti resorptive treatment (if several fractures AND a BMD Tscore < -3.5)	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months
	degraded TBS ≤ 1.200	severe osteoporosis based on WHO guidelines	very high	Ca + Vit D if needed*, anabolic treatment (if several fractures) or anti resoptive treatment	phosphocalcic chemistry test, bone turnover biomarkers and Vertebral fracture assessment by DXA or Xray	24 months

NOTE Corticosteroids will influence the global clinical assessment.

[x] major fragility fractures: upper femur fractures, humerus fractures, wirst fractures and clinical vertebral fractures (different from a symptomatic or symptomatic Xray vertebral fractures) . In some countries lower femur, upper tibial, 3 ribbs or more, pelvic fractures are also considered major fractures as well.

* based on nutrition questionnaire and 25 OH D measurement

fracture risk factors (FRF) include clinical risk factors, BMD and TBS as well as bone remodeling biomarkers

° depending on countries, a BMD/TBS test is adviced only at the end of the treatment cycle , so 4-5years (except particular situation or issue)

BMD and TBS trends (above LSC) for a menopaused woman **WITHOUT** treatment		
BMD L_{1-4} ou femur	**L_{1-4} TBS**	**Comments / Interpretation**
		• Unexpected positive trend with significant BMD and TBS increases → fracture risk reduction • Look for possible artifacts – check bone area/detection evolution from one exam to the other • No changes in patient care management
		• Expected decrease in BMD and unexpected significant TBS increase → stable fracture risk • Check clinical and biological[1] fracture risk factors(FRF) • Depending on BMD and TBS values, follow-up exam in 24 months
		• Unexpected significant BMD increase and expected TBS decrease → stable fracture risk • Check clinical and biological[1] fracture risk factors (FRF) • Look for possible artifacts – check bone area/detection evolution from one exam to the other • No changes in patient care management
		• Expected significant BMD and TBS decreases → fracture risk increased • Check clinical and biological[1] fracture risk factors (FRF) • Treatment to be evaluated based on FRF, BMD and TBS values (see previous tables) • Depending on BMD amd TBS values, follow-up exam in 24 months
		• Unexpected stable to positive evolution of BMD and TBS → slight fracture risk reduction • Look for possible artifacts – check bone area/detection evolution from one exam to the other • No changes in patient care management

		• Significant and expected BMD decrease, stable TBS → slight fracture risk increase • Check clinical and biological[1] fracture risk factors (FRF) • Treatment to be evaluated based on FRF, 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 fracture risk reduction • Check clinical and biological[1] fracture risk factors (FRF) • Look for possible artifacts – check bone area/detection evolution from one exam to the other • No changes in patient care management
		• Stable BMD and expected decrease in TBS → slight fracture risk increase • Check clinical and biological[1] fracture risk factors (FRF) • Look for possible artifacts – check bone area/detection evolution from one exam to the other • Treatment to be evaluated based on FRF, BMD and TBS values (see previous tables)
		• Expected or not, stable BMD and TBS → stable fracture risk • Look for possible artifacts – check bone area/detection evolution from one exam to the other • No changes in patient care management

[1] Devogelaer J-P et al. Is there a place for bone turnover markers in the assessment of osteoporosis and its treatment? Rheum Dis Clin N Am 2011; 37: 387-400

BMD and TBS evolution (above LSC) for a menopaused woman with OP treatment		
DMO L_{1-4} ou femur	**L_{1-4} TBS**	**Comment / Interpretation**
↑	↑	• Without any new fracture, global increase in BMD (standard effect of anabolic and some anti-resorptive treatment and micro architectural improvement, demonstrating patient compliance and treatment efficacy → fracture risk reduction • No change in patient care management • Follow-up exam in 24 months, depending on treament duration or intended pause.

↓	↑	• BMD loss, microarchitectural improvement → stable fracture risk
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors (FRF)
		• Incomplete efficacy of current treatment; consider new treatment[2]
		• Follow-up exam in 24 months

↑	↓	• BMD improvement and microarchitectural deterioration → stable fracture risk
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors (FRF)
		• Incomplete efficacy of current treatment ; consider new treatment[2]
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• BMD and microarchitectural decrease → fracture risk increased
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors
		• Incomplete efficacy of current treatment; consider new treatment[2]
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• BMD increase and stable microarchitecture (standard effect of anti-resorptive treatment) → slight reduction in fracture risk
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection and evolution from one exam to the other
		• No changes in patient care management
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• BMD decrease and stable microarchitecture → slight increase in fracture risk
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors
		• Incomplete efficacy of current treatment; consider new treatment[2]
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• Stable BMD and microarchitectural improvement → slight fracture risk reduction
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• No changes in patient care management
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• Stable BMD and microarchitectural deterioration → slight fracture risk increase
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors
		• Incomplete efficacy of current treatment; consider new treatment[2]
		• Depending on BMD and TBS values, follow-up exam in 24 months

		• Stable BMD and microarchitecture → stable fracture risk
		  ○ Check patient compliance with treatment
		  ○ Check for new fracture(s)
		  ○ Check bone area/detection evolution from one exam to the other
		• Check clinical and biological[1] fracture risk factors
		• Incomplete efficacy of current treatment; consider new treatment[2]
		• Depending on BMD and TBS values, follow-up exam in 24 months

[1] Devogelaer J-P et al. Is there a place for bone turnover markers in the assessment of osteoporosis and its treatment? Rheum Dis Clin N Am 2011; 37: 387-400

[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

Clinical cases combining both BMD and TBS

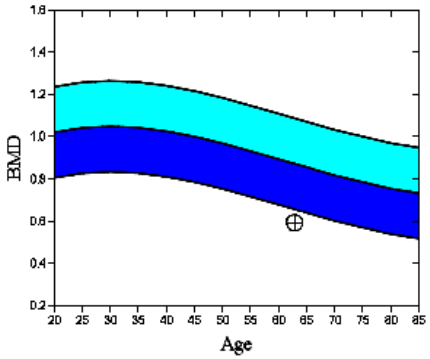
is recommended to identify discrepancies between the two examination results in absolute values, rather than as percentages. However, we have elected to express both values as percentages in this document, in order to ease the lecture and comprehension of the clinical cases.

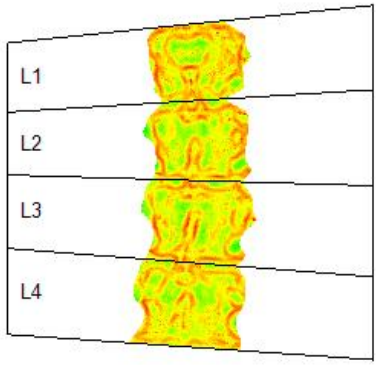
Case n°1 - Postmenopausal Osteoporosis:

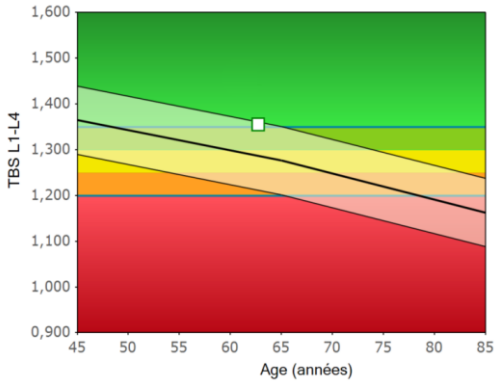
History: 63 year-old woman. No history of fracture. Menopause at age 50. HRT for 2 years. Osteoporotic mother. No smoking. Alcohol consumption: 1.5dl of wine/day (3 units?). Regular physical activity. Normal weight. Daily calcium intake: 500 to 1000 mg. History of leukemia in remission, treated with 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/Examination: 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.

Planned Monitoring/Next Examination: CTX and 25-OH vitamin D to be reassessed in one year. DXA, vertebral fracture assessment (VFA) and TBS and CTX in 2 years.

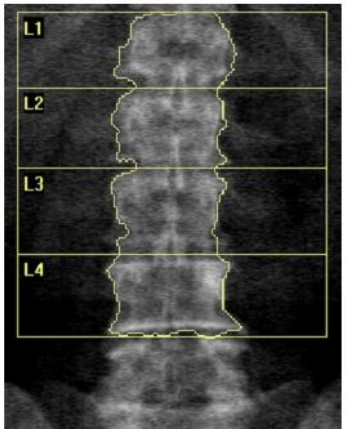
Case n°2 Densitometric osteoporosis: Treatment selection?

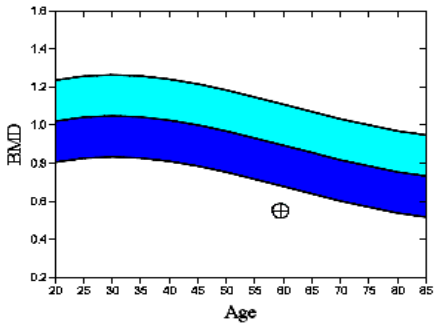
History: 59 year-old woman. No history of fracture. Menopause at age 50. Smoking habit. Regular physical activity. Normal weight. Daily calcium intake: 500 to 1 000 mg.

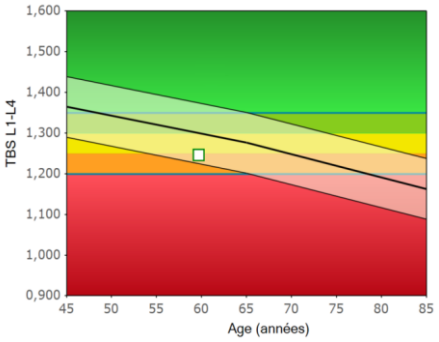
Clinical Assessment: Densitometric osteoporosis diagnosed in the context of a clinical trial/study.

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







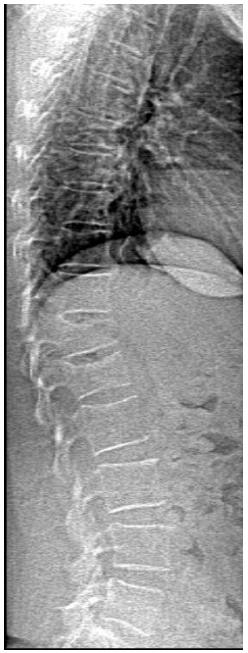
Medical Decision: In view of the very low T-score in the spine and the high CTX, we have decided to prescribe an anti-resorptive drug, despite the patient's young age and the absence of fractures. Plus, in view of partially degraded TBS, we chose to give either Prolia® (denosumab) or Protelos® (strontium 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.

Planned Monitoring/Next Examination: CTX to be checked in 3 months. CTX and 25-OH vitamin D in one year. DXA, VFA, TBS and CTX in two years.

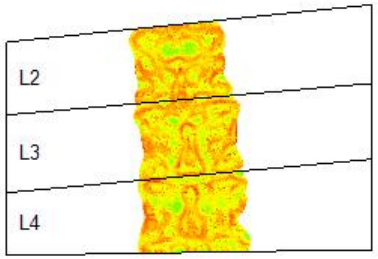
Case n°3 - Early menopause and vertebral fracture:

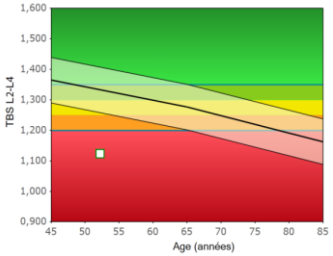
History: 52 year-old woman. No history of fracture. Early menopause at the age of 40. Active smoker. No HRT. In good general health.

Clinical assessment: Three spontaneous vertebral fractures. Malignancy screen: negative. (bone biopsy: porous bone).



Bone Assessment /Examination: Spine BMD T-score -2.8 SD, Total Hip BMD T-score -2 SD and Femoral Neck BMD T-score -2.1 SD. **TBS result: 1.120**.





Medical Decision: In view of the clinical assessment and TBS results, treatment with 18 months of teriparatide is immediately initiated (it is important to note that, in some countries, teriparatide is reimbursed only as a secondary option, in cases of unsuccessful preliminary use of an anti-resorptive agent. In those countries, an anti-

resorptive drug known for its positive influence on bone microarchitecture could be prescribed).

Planned Monitoring/Next Examination: 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 countryThis case emphasizes how smoking and early menopause both can have a major negative impact on bone microarchitecture.

Case n°4 - Osteopenia and vertebral fracture:

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

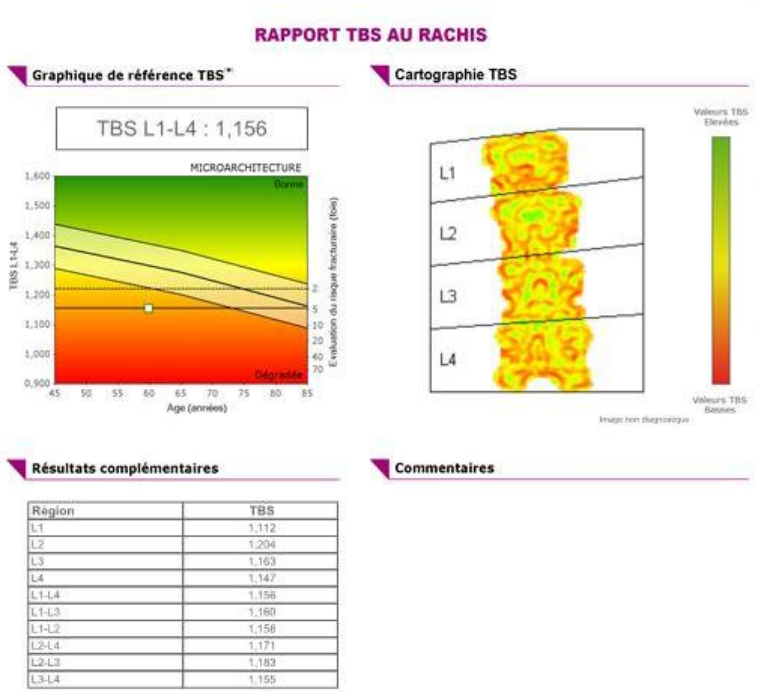
Clinical Assessment: No fracture. Physiological menopause; no other associated risk factors for fracture.

1st Bone Examination: 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.

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.

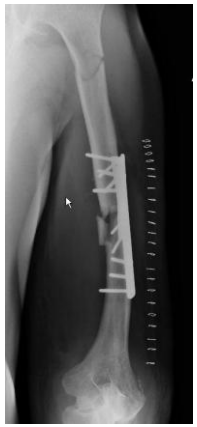
Planned Monitoring/Next Examination: DXA, VFA and TBS in 24 months.

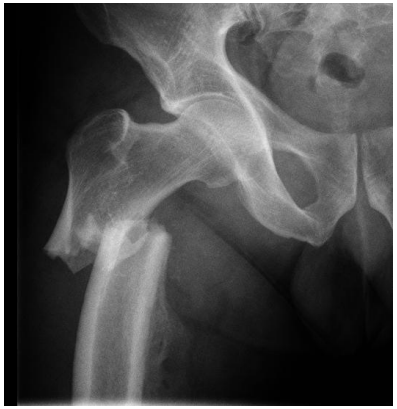
Case no 5 - Osteogenesis imperfecta:

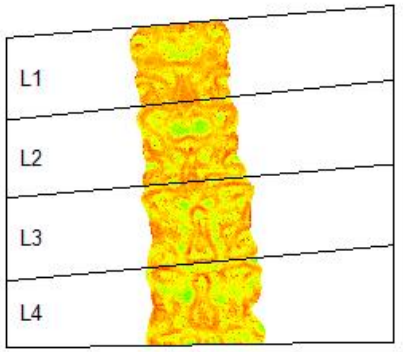
History: 55 year-old man diagnosed with type IV osteogenesis imperfecta several years previously. Sustained 40 fractures and had frequent surgery throughout childhood and adolescence. No more fractures then until the age of 46, when he fractured his scapula. At the age of 53, he had a traumatic bifocal fracture of the left humerus and a right sub-trochanteric 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/m^2. His BMD values have been stable over the past few years.

Bone Examination: 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.

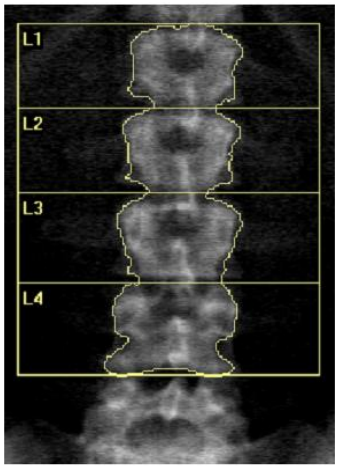
Planned Monitoring/Next Examination: DXA and TBS in 24 months, even while recognizing that the patient is not currently under any treatment.

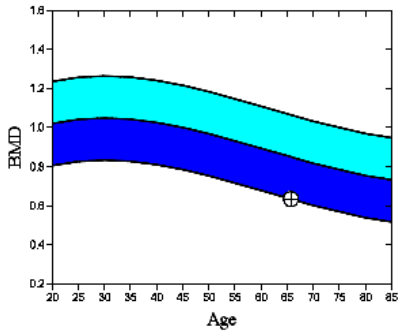
Case no 6 - HIV and bone:

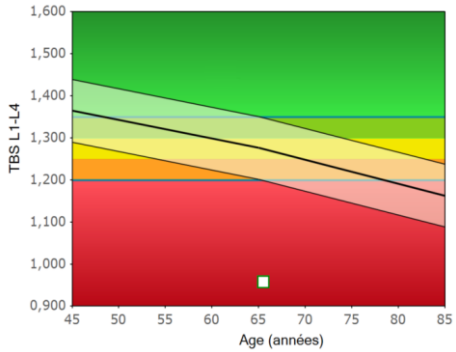
History: 66 year-old woman with stage A2 HIV infection diagnosed 15 years ago, treated with several anti-retroviral drugs. Hepatic steatosis and metabolic syndrome. At risk for alcohol use. History of hyperthyroidism from Graves' disease. Weight: 75.5 kg; Height: 160 cm; BMI 29.49 kg/m^2.

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 Examination: 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 Examination: 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.

Planned Monitoring/Control Examination: DXA and TBS in 24 months to evaluate the potential initiation of teriparatide.

Case no 7 - Vitamin D Deficiency and vertebral fracture:

History: 67 year-old woman with normal BMI. Menopause at 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 Examination: 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 Examination: 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.

Planned Monitoring/Control Examination: DXA and TBS in 24 months.

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

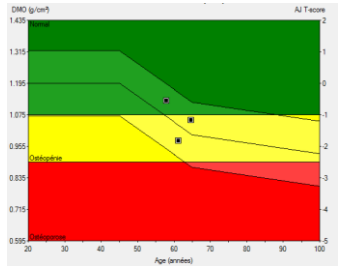
Case no 8 - Follow-up of corticosteroid-induced osteoporosis:

History: 64 year-old woman. Menopause at 51 years old. Fractures at D10 and D12. Height: 165 cm; weight: 71.7kg BMI 26.3kg/m^2. Polymyalgia rheumatica (PMR) diagnosed 10 years ago, and has been on 7.5 to 10 mg/day prednisone ever since. No monitoring or preventative 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 examination:

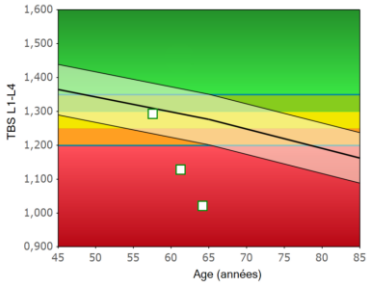
- 1st examination in 2004: bone mineral density normal in the spine and hip, and no fractures detected on VFA.
- Follow-up visit in 2008: significant bone loss in the spine : -14.1% (beyond LSC), with -5.3% bone loss in the hip. No fracture by VFA → Initiation of treatment with alendronate 70 mg/week.
- Follow-up visit in 2011: significant gain in the spine of +9.0% (beyond LSC), with +3.3% gain in 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).

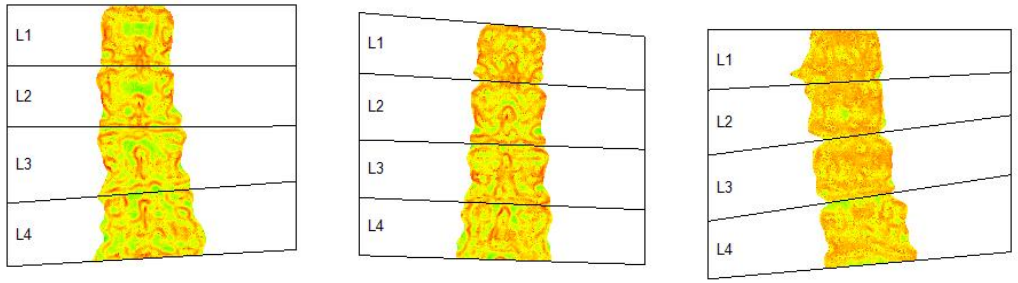


Medical Decision: The increase in bone mineral density was reassuring, but the discovery of an unexpected vertebral fracture after two years of treatment left us confused about this case. The patient's weight was stable between 2004 and 2011. It was decided to retrospectively analyse TBS values corresponding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

Retrospective Bone Examination:

- Retrospective examination, 2004: TBS = 1.290 (partial architectural degradation).
- Retrospective examination, 2008: TBS = 1.135 (degraded) → significant loss of -12% (beyond LSC)
- Retrospective examination, 2011: TBS = 1.031 (highly degraded) → additional significant loss of -9.2% (beyond LSC)





New 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.

Planned Monitoring/Next Examination: biological markers in 3 months to verify treatment compliance. DXA and TBS in 24 months.

Case no 9 - Treatment with an aromatase inhibitor and Os:

History: 62 year old woman. Menopause at age 46. No hormone replacement therapy. Height: 159 cm; weight 73 kg, with BMI = 28.87 kg/m^2. Breast cancer in 2010, treated with surgery, radiotherapy and an aromatase inhibitor.

Clinical assessment: No vertebral fractures. No tobacco. Normal alcohol consumption. Dietary calcium intake between 500 and 1000 mg/day. Hip fracture in the mother. FRAX value of 11.1% for major osteoporotic fracture.

Initial bone assessment and monitoring:

- 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
- TBS
  - Microarchitecture partially degraded in 2010 with a TBS = 1.260

- Monitoring visit in 2012 (relative to 2010): significant -9.5% loss by TBS. The patient exhibited markedly deteriorated bone microarchitecture.

Support: Given the significant losses in BMD and TBS, a specific anti-resorption drug 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.

Planned Monitoring/Next Examination: Biomarkers in three 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.

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