Beyond bone mineral density: new developments in dual X-ray absorptiometry assessment of bone quality

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ABSTRACT

Bone mineral density, bone texture, bone geometry and bone strength are all elements necessary for a proper osteoporotic fragility fracture prediction assessment. Data regarding bone quantity (density) and, in part, bone quality (structure and geometry) are obtained by the gold standard method of dual X-ray absorptiometry (DXA), while data about bone strength are obtained by means of a new DXA index called the bone strain index (BSI). The BSI evaluates bone resistance by means of average strain calculation, and it is based on finite element analysis applied to DXA spine and femoral scans. The BSI includes local information on bone density distribution, bone geometry and, unlike variables of bone mineral density and bone quality such as the trabecular bone score, it represents the status of the bone in a particular loading condition. This review illustrates the methodology for calculating the BSI and discusses findings on its reproducibility and data about its capability to predict fragility fractures and monitor pharmacological treatment for osteoporosis.

KEYWORDS

DXA, BSI, TBS, BMD, FEM, HSA

Introduction

The dual X-ray absorptiometry (DXA) method is the gold standard for assessing bone quantity (bone mineral density, BMD), bone quality (trabecular bone score, TBS), and bone geometry (hip structure analysis, HSA) [1-3]. Osteoporosis is diagnosed when BMD, expressed in standard deviations from a healthy young population, is ≤-2.5 for postmenopausal women and for men aged over 50 years, while osteopenia is defined as a T-score ≤-1.0. In all the other cases, BMD is expressed as standard deviations from the age- and sex-matched population with the cutoff set at ≤-2.0 [4].

Besides DXA, other methods for investigating bone status are quantitative computed tomography [5] and quantitative ultrasound [6], which have been applied for several years in osteoporosis management, and recently a radiofrequency echographic technique based on the analysis of raw ultrasound signals [7-9]. However, DXA is still the gold standard method for assessing bone status.

Skeletal sites affected by bone derangement in osteoporosis are those with cortical bone, like the femoral neck and distal radius, and with prevalently trabecular bone, like the lumbar spine [10,11], with significantly lower BMD values related to disease duration, regardless of treatment [12]. Glucocorticoids (GCs) are the main drugs showing a detrimental effect on bone with an increased risk of fragility fracture documented in the literature [13]. However, the occurrence of fragility fractures in patients treated with GCs who have normal or slightly reduced BMD, and in postmenopausal women with normal or slightly reduced BMD, raises the question of whether bone factors other than density are relevant for a better comprehension of bone failure [14]. The TBS, an indirect DXA index of bone texture, appears to be an index of bone quality that may explain fracture events at higher BMD in patients receiving GCs [13,15]. Moreover, the TBS has been shown to discriminate osteoporotic patients and predict fragility fractures independently of BMD [2]. However, as a lumbar spine textural index, the TBS does not provide all the data necessary to evaluate the resistance of bone to compressive, torsional and flexural loads. Hip geometry is another useful aspect that could help to shed light on the reasons for bone failure. HSA is based on a DXA femoral scan, and it provides parameters that can be useful for assessing femoral bone resistance to flexural and torsional loads [16]. Notwithstanding this, there is still no clear evidence that HSA is helpful in predicting fragility fractures [17].

BMD, TBS and HSA (particularly BMD) are undoubtedly useful in assessing bone status, but they are unable to provide complete information about bone resistance to load, when data relating to strength are missing. A new DXA-derived index has recently been developed. Named the bone strain index (BSI), it is based on finite element analysis applied to a greyscale of density distribution measured on spine and femoral scans. The BSI includes local information on density distribution, bone geometry and loading, and therefore differs from BMD and

Article history
Received 11 May 2021 – Accepted 25 Oct 2021

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also from other variables of bone quality like the TBS, which are based on the quantification of bone mass and distribution, averaged over the scanned region. The BSI appears to be a new frontier in bone assessment that could allow better understanding of bone quality derangement in metabolic bone diseases. This review looks at the methodology of BSI calculation, findings regarding its reproducibility, and data on its capability to predict fragility fractures and to monitor pharmacological treatment for osteoporosis.

Beyond bone mineral density

Background

Bone can be considered a complex object, built with particular structural and geometrical characteristics to fulfil its natural support function, that is to say, resistance to loads: compressive, torsional and flexural.

In a structure subject to an external load, the magnitude and distribution of internal stresses depend not only on the loading configuration but also on the geometry of the structure and its material properties. Stresses and strains have to remain below a specific level, named the yield point, in order to avoid permanent damage and fracture. Bone, too, is subject to these same mechanical rules and its resistance is governed by its density, geometry, internal trabecular structure, and cortical thickness, all of which can be inferred from radiological images.

The quantification of these features can be based on 3D data, for example, in the case of computed tomography, or 2D data, where traditional radiography (X-ray) and DXA are the most common technologies.

Image data coming from a radiological device can be analysed using different methods [18-20], ranging from classic beam models, usually applied to long bones [18,21,22], to the more recent mathematical approach called the finite element model (FEM) [23]. The FEM method consists of dividing an object into simpler elements, to which the laws of classical mechanics apply. Forces and constraints that act on specific areas of the system generate internal stresses and strains depending on the amplitude and directions of the forces themselves, on the system geometry, and on the material properties assigned to each element.

Although many FEMs have been developed to investigate bone status and fracture risk, they are not really used in routine clinical practice. Indeed, the FEM programmes implemented to date have not been completely automated, and nor are they really adapted to clinical reporting. Furthermore, it is important to apply this method to both the femoral and the lumbar anatomical sites usually scanned using DXA. Nevertheless, recent studies have demonstrated that FEMs are better experimental vertebral strength predictors than areal BMD measured with DXA [24].

A new FEM-based DXA parameter, the BSI, has been recently introduced [25]. The Authors demonstrated a good correlation between calculated yield strain and experimental yield measured on porcine vertebra samples. The same algorithm was then applied to human vertebrae, with a model thickness dependent on the average width of the vertebra, and an elastic modulus assigned to each element according to experimental equations [26].

Due to its high accuracy, low cost and low radiation exposure, as well as the widespread availability of bone densitometry, DXA is the gold standard method for assessing and monitoring bone status in clinical practice [27]. The BMD measured is an areal density (g/cm^2) and, given the projective nature of the DXA device, it is dependent on bone mineralisation (and thus on volumetric BMD), and on the bone quantity exposed to the X-ray, which in turn is related to bone thickness [22]. BMD is routinely used in clinical practice to classify patients into risk classes depending on the epidemiological criterion of BMD distribution in healthy subjects and patients affected by fragility fracture [28]. BMD is also used to evaluate patient response to pharmacological treatment prescribed to reduce fracture risk. However, BMD does not entirely explain fracture risk since many fractures still occur in populations with normal or slightly reduced bone mass [29].

From a construction point of view, many other factors of the skeleton should be considered to explain bone strength [30] and to improve our ability to predict structural failure. BMD provides a valuable measure of the material properties, but the internal structure is equally important to investigate when seeking to understand the capability of the construction to withstand an external load.

Trabecular bone score

The TBS is a densitometric index automatically provided for lumbar DXA scan analysis. The TBS evaluates bone mineral variations in lumbar DXA images in order to describe the bone's internal structural distribution.

TBS calculation is based on the idea that brighter areas on a DXA image indicate a dense bone matrix, whereas dark areas describe a structure with low connectivity, low trabecular number, and large spaces between the trabeculae [31].

Being based on lumbar DXA planar images, the TBS can explain spine porosity and density variation only in the frontal plane (Fig. 1). On the other hand, unlike BMD, which measures the average bone quantity in a given area, the TBS represents the spatial variation of bone and can discriminate between patients with similar BMD, but different trabecular microarchitecture.

So, while BMD measurement tells us the average bone mineral content projected over a defined area, TBS calculation depends on how the bone mineral content is distributed over that same projection.

In the literature, the TBS has been shown to discriminate fractured patients and predict fracture partially independently of BMD [32]. More recently, the literature has demonstrated that the TBS is also helpful in monitoring pharmacological treatment of osteoporosis [33]. Recently, its behaviour has been investigated on DXA images other than of the lumbar spine [34,35], giving promising results that further research might confirm.

Hip geometry

Geometry and size are parameters that govern the mechanical resistance of bone [36]. In recent years, the HSA algorithm has been proposed to provide a structural description of the proximal femur, and further improve fracture prediction [22]. This

algorithm automatically extracts geometrical information from proximal femur DXA images, providing mechanical parameters in three regions of interest: the so-called narrow neck, inter-trochanteric, and femoral shaft regions. For each region, mechanical properties are derived from femur geometry and calculated distribution of bone mass (Fig. 2).

HSA parameters are: the cross-sectional area (CSA) of the bone surface; the cross-sectional moment of inertia (CSMI), which describes how the bone mass is distributed around the femoral axis; and the section modulus (Z), which represents the maximum bending stress.

HSA software works on the assumption that compression load forces are uniformly distributed over the CSA. On the other hand, under bending conditions, the resistance of bone is proportional to the square of the distance from the neutral axis. Therefore, bone strength is affected much more by bone near the outer surface than by bone near the femoral axis.

Since the main kinds of stress acting on the femoral site are compression and bending [37], the higher the CSA and CSMI are, the better bone resistance will be.

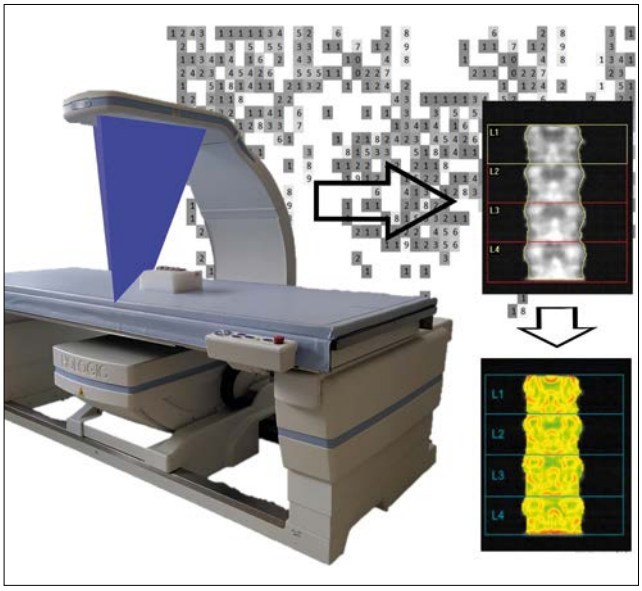
Among the parameters provided by HSA, the buckling ratio, i.e., the ratio of the outer radius to the cortical thickness, has also been shown to play an important role. If this ratio exceeds a factor of 10, rising local instability leads to a decrease in strength in the cross-section [22].

Studies have shown that HSA results predict hip fracture occurrence [38,39]. However, its use in the management of patients is still limited by difficulties interpreting the structural parameters and the lack of evidence from clinical practice settings regarding fracture prediction [2].

The International Society for Clinical Densitometry (ISCD) guidelines recommend that HSA parameters not be used to assess hip fracture risk [17].

DXA images can automatically obtain two other geometric parameters: the neck shaft angle (NSA) and hip axis length (HAL), where the latter is defined as the distance from the inner pelvic brim to the greater trochanter. Several studies have found a positive association between a longer HAL and hip fracture. It thus seems that this geometric parameter can play an important role in predicting hip fracture independently of BMD [17]. On the other hand, it is not yet clear whether the NSA can be used in clinical practice as an additional fracture risk parameter [17].

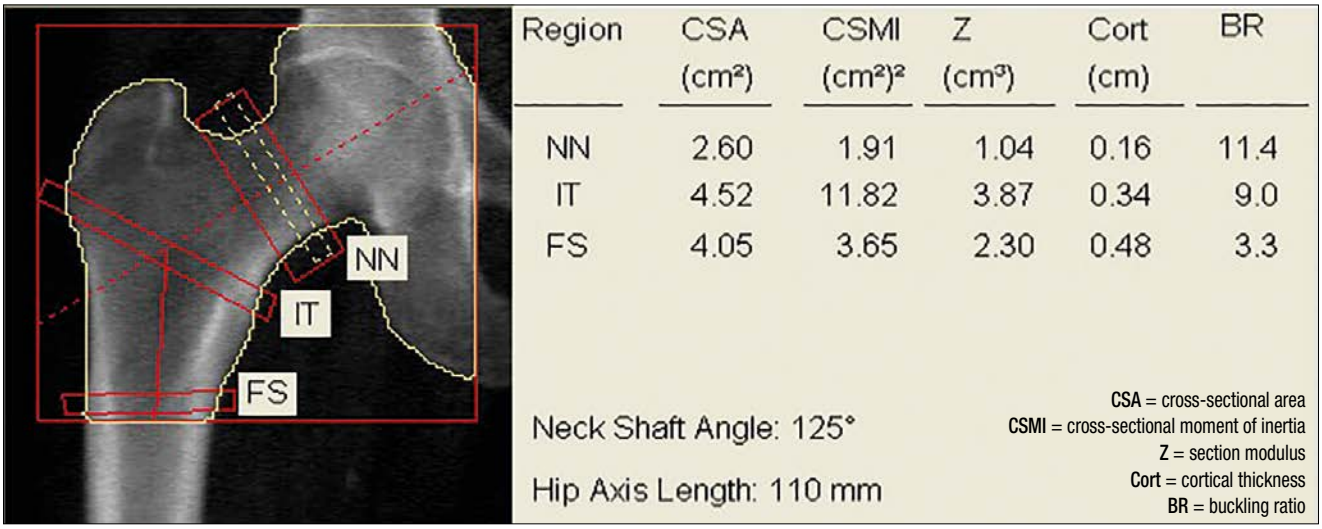
Figure 1 DXA device and acquired scan. The image resulting from DXA acquisition represents the projection of the bone in the frontal plane, and is analysed to extract BMD and TBS values.



A New Index of Bone Strength: the Bone Strain Index

In recent years, many studies have focused on FEM analysis of the proximal femur as a means of estimating femoral strength and assessing hip fracture risk. However, only a few studies have dealt with the lumbar anatomical site [20,40]. Recently, a new DXA bone parameter, the BSI, based on lumbar scan FEM analysis, has been proposed to improve fracture risk prediction considering all the features involved in bone strength [25,41]. The FEM analysis is conducted automatically, starting from a triangular mesh built upon the contour of the bone segmented by

Figure 2 Hip image from a Hologic DXA scanner showing analysis regions of the femur, namely the narrow neck (NN), intertrochanteric (IT) and shaft (FS) regions.



DXA software. Then a separate model for each vertebra is used with the load applied to the upper plate and constraints to the lower plate, according to the method used by Colombo *et al*. [25]

Material properties of each triangle of the model are assigned following the experimental relations provided by Morgan *et al*. at the lumbar site [26], whereas the force acting on the upper plate of the vertebra is calculated using the patient-specific model described in the study by Han *et al*. [42] where forces and moments acting in the spine have been calculated for various combination of body height and weight.

In the femoral region, BSI calculation is based on the hypothesis of a sideways fall condition with constraints placed on the head and the lower part of the shaft, and a subject-specific impact force applied to the greater trochanteric area [43].

BMD, TBS and BSI analysis, describing different aspects of the image, give the physician a full picture of the bone status. To better understand the significance of each tool and the information provided to the clinician, we have to consider the bone in its natural context with all the structural implications that this entails.

As shown in figure 3, BMD describes the material (e.g., vertebrae with different degrees of mineralisation), whereas TBS shows the particular internal architecture of the bone. In both representations, geometry and patient load do not influence the BMD and TBS results. As briefly explained in the introduction, mechanical resistance to fracture should consider all the above variables.

Since the BSI value is related to the capability to withstand an applied load, it should be described as a bone strength value.

Figure 4 compares DXA, TBS and BSI images. The TBS image shows the areas with low TBS values in red and those with high TBS values in green. TBS value is based on the grey-scale variations related to the trabecular structure, as previously explained. The BSI heatmap, conversely, represents the strain level inside the bone with a scale running from low (blue/green) through medium (yellow) to high (red) levels, as shown in figure 5.

No TBS-like evaluation has yet been developed for the proximal femur trabecular structure, since trabecular distribution in the region is more complex and governed by compression and tension lines. Conversely, BSI calculation for the femoral region has to rely on the same method used for the lumbar region, with material properties and boundary conditions adjusted for that site.

Figure 3 Example of the levels of information provided by BMD, TBS and BSI related to a man sitting on a vertebra. Figures **a** and **b** show material differences as assessed by BMD DXA (i.e., different degrees of bone mineralisation). Figures **c** and **d** relate to internal structure and show how the same TBS approach highlights the difference between a sparse and a dense structure. Figures **e** and **f** show the stress-strain status of two vertebrae with different densities, structure and geometry, with two different people with different weight sitting on the top. The information in e and f is provided by BSI.

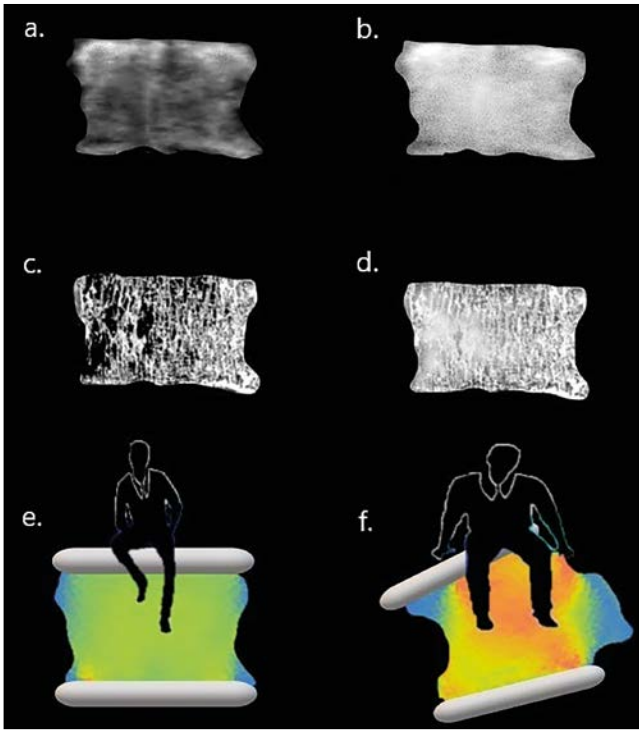


Figure 4 Example of images provided by DXA: BMD L1L4 =0.77 g/cm^2 (left); TBS L1-L4=1.291 (center) and BSI L1L4 = 2.14 (right).

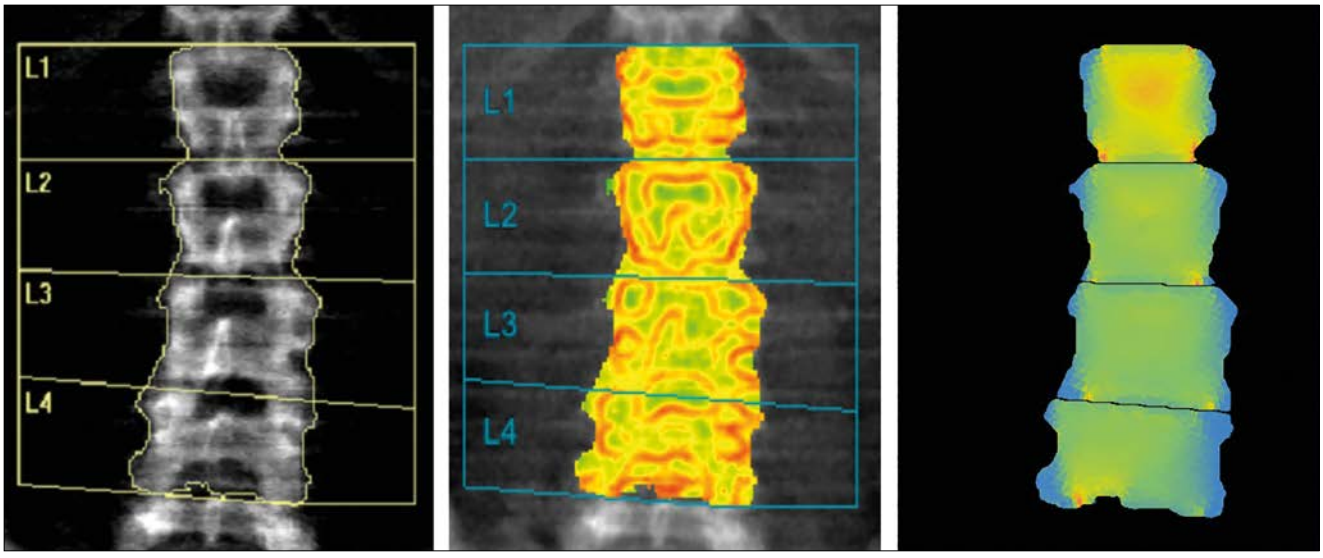


Figure 5 shows an example of left femur BSI analysis with the representation of forces and constraints.

Recent clinical studies have investigated the usefulness of BSI in identifying osteoporotic patient subgroups particularly prone to fragility fractures [17] and in predicting further fragility fractures [45,46] (Tab. I). The Authors, using artificial neural network analyses (ANNs), investigated 125 consecutive postmenopausal women, assessing DXA parameters, biochemical markers of bone turnover, and clinical data. A low fracture risk appeared to be related to a low carboxy-terminal cross-linking telopeptide of type I collagen level, whereas a positive Romberg test, together with a compromised bone strength DXA (high lumbar BSI), appeared to be closely connected with fragility fractures, indicating the path that leads to fragility fracture in a postmenopausal population [44]. More recently, Messina *et al*. demonstrated that lumbar BSI is an independent predictor of a subsequent fragility re-fracture [46]. The Authors investigated 234 consecutive fractured patients with primary osteoporosis. They performed a spine X-ray for calculation of the spine deformity index (SDI) and a DXA test for baseline and follow-up BMD, TBS and lumbar BSI measurements. A subsequent fracture was defined as one unit increase of SDI. For each unit increase of the investigated indexes, the univariate hazard ratio of re-fracture, 95% CI, p-value and proportionality test p-value were: for age 1.040; 1.017-1.064; 0.0007; 0.2529, respectively, and for lumbar BSI 1.372; 1.038-1.813; 0.0261; 0.5179, respectively. Lumbar BSI remained in the final multivariate model as a statistically independent predictor of a subsequent re-fracture (1.332; 1.013-1.752; 0.0399) together with age (1.039; 1.016-1.064; 0.0009). The multivariate model proportionality test p-value was 0.4604.

It was recently shown that lumbar BSI appeared able to characterise young patients affected by secondary osteoporosis [44,47] (Tab. I). In a cohort of patients affected by mastocytosis [96 consecutive patients (46 women and 50 men) affected by cutaneous or systemic mastocytosis], the Authors found a correlation between lumbar BSI and severity of bone deterioration. Tryptase was inversely correlated with lumbar BMD (r=-0.232; p=0.022) and TBS (r=-0.280; p=0.005), and directly with lumbar BSI (r= 0.276; p=0.006). Lumbar BSI remained statistically significant (p= 0.006; adjusted R^2= 0.101) in the multivariate regression model with tryptase as a dependent variable, as lumbar BMD and TBS were not statistically significant. Tryptase increased by about 22 units for each unit increase of lumbar BSI. Moreover, lumbar BSI was statistically significantly lower in women than in men, suggesting that men have worse lumbar bone resistance to compressive loads, in line with the more severe bone involvement in mastocytosis in the male sex [47] (Tab. I).

Another aspect found to characterise DXA as the gold standard method for diagnosing and monitoring osteoporosis was its higher reproducibility and precision [48]. Precision is defined by the International Society for Clinical Densitometry as the ratio between standard deviation and mean (CoV). Per cent least significant change (LSC%) is calculated as 2.77 × CoV, and reproducibility is calculated as the complement to 100% of LSC% [4]. BMD reproducibility is usually the standard of reference for other DXA-based measurements and this has been confirmed in a recent work [49,50]. BMD reproducibility was around 99% in all the densitometric scan modalities, while the reproducibility of BSI was lower than that of BMD, as its CoV was between 0.6% and 1.4% and LSC about three times higher than that of BMD.

Table I provides an overview of BMD and BSI *in vitro* and *in vivo* precision. With regard to *in vivo* results, a comparison between different BMI groups and different waist circumferences was reported in a study by Messina *et al*., in which the difference between BMD and BSI reproducibility was almost the same as that found in the previous phantom study [51]. Moreover, the reproducibility of all DXA parameters has been found

Figure 5 Examples of left femur BSI analysis with representation of forces and constraints. The heat map related to the strain distribution shows a major strain concentration on the red area. The head of the femur is not represented because the coloured regions represent the same regions identified by DXA analysis (neck, intertrochanteric and trochanteric).

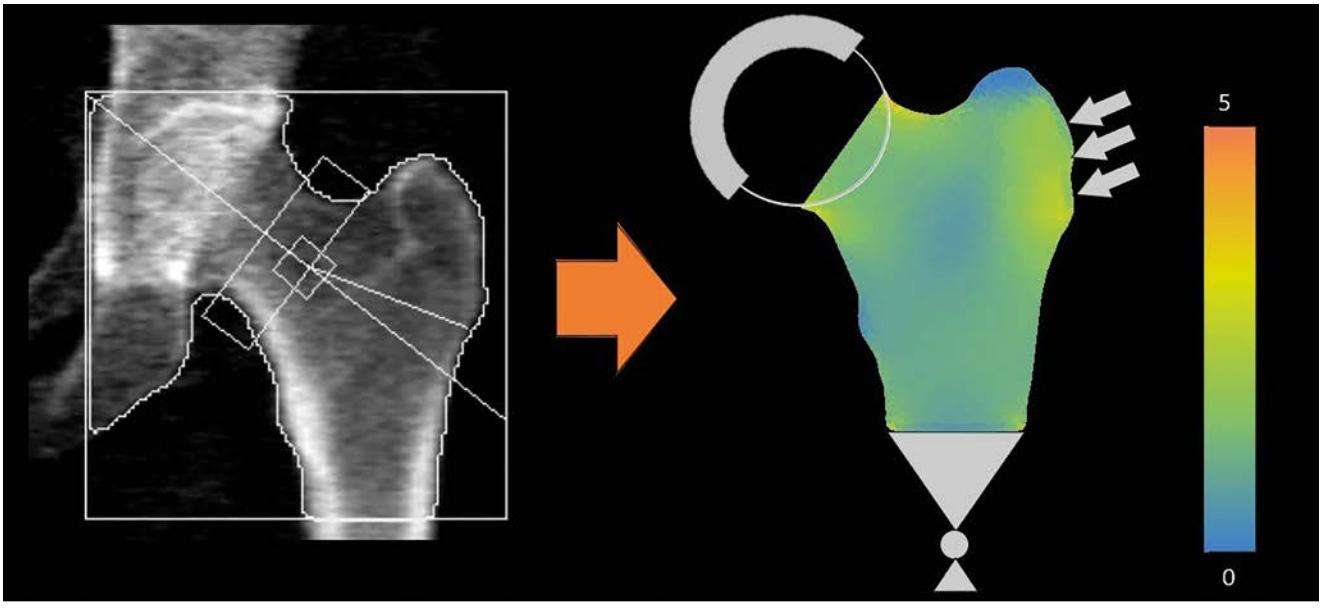


Table I

TOPIC	AUTHOR	YEAR	N. PTS	MAIN FINDINGS
BSI in hyperparathyroidism	Tabacco *et al.*	2021	150	BSI was significantly higher at LS (2.20±0.58 *vs* 1.94±0.48, p=0.003), FN (1.66±0.39 *vs* 1.40±0.36, p=0.003) and TH (1.46±0.3 *vs* 1.24 ±0.25, p=0.001) in PHPT. LS-BSI showed moderate accuracy for discriminating VFs (AUC 0.667; 95% CI 0.513-0.820), LS-BSI ≥ 2.2, and was a statistically significant independent predictor of VFs.
Prediction of vertebral refracture (artificial intelligence-based analysis)	Ulivieri *et al.*	2021	172	ANN resulted in an accuracy of 79.36%, with a sensitivity of 75% and a specificity of 83.72%. The first bone variable directly related to the event (further fracture, no further fracture) was found in LBSI, indicating that declining bone strength (LBSI high) is a significant risk factor for further VF.
BSI hip reproducibility	Messina *et al.*	2020	30	BSI precision was about three times higher than that of BMD, confirming previous results of lumbar spine BSI. *In vivo* reproducibility of total femur (CoV = 3.89%, reproducibility = 89.22%) was better than that of the femoral neck (CoV = 4.17%, reproducibility = 88.46%).
Prediction of vertebral refracture (multicentric retrospective study)	Messina *et al.*	2020	234	BSI hazard ratio of incident re-fracture (95% CI) was 1.372 (1.038–1.813), p value = 0.0261, proportionality test p value: 0.5179.
Bone geometry and structural indexes in mastocytosis (retrospective study)	Ulivieri *et al.*	2020	96	Tryptase showed a statistically inverse correlation with lumbar spine BMD (r = -0.2326; p = 0.0226) and with TBS (r = -0.2801; p = 0.0057) and a direct correlation with lumbar BSI (r = 0.2759; p = 0.0065). In the final multivariate regression model, only the lumbar BSI in systemic mastocytosis (p = 0.0064) and non-systemic mastocytosis (p = 0.0338) remained statistically significant.
Prediction of vertebral refracture (retrospective study)	Ulivieri *et al.*	2020	143	The hazard ratios of refracture for each unit increase of BSI, BMD and TBS were 1.201, 0.231 and 0.034, respectively. BSI proved to be the nearest to statistical significance in predicting a refracture, with greater values associated with a higher refracture risk.
DXA parameters: response to teriparatide (retrospective study)	Messina *et al.*	2020	40	In the entire population, improvements after therapy were seen in BSI (-13.9%), TBS (5.08%), BMD (8.36%). Significant HSA variations were seen only at the femoral shaft, but were very small (FS_BMD (0.23%), FS_CSA (-0.98%), FS_SEC_MOD (-2.33%) and FS_BR (1.62%)).
In vivo reproducibility	Messina *et al.*	2020	150	BSI best reproducibility value was observed in group with BMI between 25 and 30 kg/m^2 (CoV 1.97%, reproducibility 94.5%), while the worst was in the group with BMI > 30 kg/m^2 (CoV 3.96%, reproducibility 89.0%). BSI reproducibility progressively worsened from lower BMI to higher BMI, but the amount of this reduction was never statistically significant.
In vitro reproducibility and influence of soft tissue thickness	Messina *et al.*	2019	Phantom based study	The highest BSI reproducibility value was 98.3% (1-cm soft tissue thickness, HD-mode), whereas the lowest was 96.1% (6-cm soft tissue thickness, HD-mode). Variations between scans with superimposed 0-6-cm soft tissue thickness were between 0.76% and 1.46% for BMD, and between 1.03% and 1.57% for BSI.
DXA-derived parameters in haemophilic patients (retrospective study)	Ulivieri *et al.*	2018	70	A reduced bone mass was present at the femoral neck in 55.7%, at the total femur in 18.6%, and at the lumbar spine in 54.3% of patients. Lumbar spine BMD, TBS and BSI did not correlate with HJHS (Haemophilia Joint Health Score). HSA bone geometric parameters correlated negatively with HJHS.
Clinical observational retrospective study	Ulivieri *et al.*	2018	125	A low fracture risk seems to be related to a low carboxy-terminal cross-linking telopeptide of type I collagen level, whereas a positive Romberg test, together with compromised DXA parameters, appeared to be closely connected with fragility fractures. Compromised BSI together with positive Romberg test characterises the pathway leading to fracture in postmenopausal women.

to worsen slightly in obese patients and in those with a greater waist circumference. This pattern can be explained by the soft tissue superimposed on the bone, which affects the X-ray image by generating noise and reducing image quality and accuracy [52]. The ability of BSI to monitor the effect of anabolic treatment for osteoporosis has been assessed in a recent clinical validation study [53]. Forty osteoporotic patients with fractures were studied before and after two years of daily subcutaneous 20 mcg of teriparatide. BMD, HSA, TBS and BSI were measured and analysed by means of classical statistical approach and ANNs were used for the analysis. The Authors demonstrated significant improvements, after therapy, in BSI (-13.9%), TBS (5.08%), BMD (8.36%). Dividing patients into responders and non-responders on the basis of BMD increase >10%, the first group presented TBS and BSI improvements (11.87% and -25.46%, respectively), while the second group showed improvement of BSI only (-6.57%). This finding suggests that an increase in bone strength may explain the known reduction in fracture risk not completely justified by BMD increase.

The future of DXA

Osteoporosis is characterised not only by bone quantity but also bone quality impairment. For a complete assessment of bone status, in addition to the amount of bone, it is necessary to have information on its spatial distribution, geometry and strength, as these elements contribute to determining skeletal

resistance to load and fatigue.

The TBS is a widely studied bone textural index that discriminates fractured patients and predicts fracture both in primary and secondary osteoporosis where bone architecture is damaged. Even though femur size and shape have been shown to be critical for the mechanical strength of the hip under various loading conditions and HAL shows good results in fracture risk prediction in postmenopausal women, HSA needs further evidence. Bone strength is the last area where there is still a need for knowledge useful for understanding all the physical implications of bone resistance to loads and fatigue, so as to provide clinicians with all they need in order to better manage osteoporotic patients.

BSI appears to be an index of bone strength that will provide the missing information on the skeletal resistance to the loads.

References

1. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser.1994;843:1-129.
2. Silva BC, Broy SB, Boutroy S, Schousboe JT, Shepherd JA, Leslie WD. Fracture Risk Prediction by Non-BMD DXA measures: the 2015 ISCD official positions Part 2: trabecular bone score. J Clin Densitom. 2015;18(3):309-30.
3. Beck TJ, Broy SB. Measurement of hip geometry-technical background. J Clin Densitom. 2015;18(3):331-7.
4. Lewiecki EM, Gordon CM, Baim S, et al. International Society for Clinical Densitometry 2007 adult and pediatric official positions. Bone. 2008;43(6):1115-21.
5. Zysset P, Qin L, Lang T, et al. Clinical use of quantitative computed tomography-based finite element analysis of the hip and spine in the management of osteoporosis in adults: the 2015 ISCD official positions-Part II. J Clin Densitom. 2015;18(3).
6. Hans D, Baim S. Quantitative Ultrasound (QUS) in the management of osteoporosis and assessment of fracture risk. J Clin Densitom. 2017;20(3):322-33.
7. Adami G, Arioli G, Bianchi G, et al. Radiofrequency echographic multi spectrometry for the prediction of incident fragility fractures: a 5-year follow-up study. Bone. 2020;134:115297.
8. Di Paola M, Gatti D, Viapiana O, et al. Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. Osteoporos Int. 2019;30(2):391-402.
9. Diez-Perez A, Brandi ML, Al-Daghri N, et al. Radiofrequency echographic multi-spectrometry for the in-vivo assessment of bone strength: state of the art-outcomes of an expert consensus meeting organized by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Aging Clin Exp Res. 2019;31(10):1375-89.
10. Haugeberg G, Helgetveit KB, Førre Ø, Garen T, Sommerseth H, Prøven A. Generalized bone loss in early rheumatoid arthritis patients followed for ten years in the biologic treatment era. BMC Musculoskelet Disord. 2014;15:289.
11. Węgierska M, Dura M, Blumfield E, Żuchowski P, Waszczak M, Jeka S. Osteoporosis diagnostics in patients with rheumatoid arthritis. Reumatologia. 2016;54(1):29-34.
12. Mori Y, Kuwahara Y, Chiba S, et al. Bone mineral density of postmenopausal women with rheumatoid arthritis depends on disease duration regardless of treatment. J Bone Miner Metab. 2017;35(1):52-7.
13. Compston J. Glucocorticoid-induced osteoporosis: an update. Endocrine. 2018;61(1):7-16.
14. Ulivieri FM, Silva BC, Sardanelli F, Hans D, Bilezikian JP, Caudarella R. Utility of the trabecular bone score (TBS) in secondary osteoporosis. Endocrine. 2014;47(2):435-48.
15. Chuang MH, Chuang TL, Koo M, Wang YF. Trabecular bone score reflects trabecular microarchitecture deterioration and fragility fracture in female adult patients receiving glucocorticoid therapy: a pre-post controlled study. Biomed Res Int. 2017;2017:4210217.
16. Wright NC, Lisse JR, Beck TJ, et al. Rheumatoid arthritis is associated with less optimal hip structural geometry. J Clin Densitom. 2012;15(1):39-48.
17. Broy SB, Cauley JA, Lewiecki ME, Schousboe JT, Shepherd JA, Leslie WD. Fracture risk prediction by non-BMD DXA Measures: the 2015 ISCD official positions Part 1: hip geometry. J Clin Densitom. 18(3):287-308.
18. Mourtada FA, Beck TJ, Hauser DL, Ruff CB, Bao G. Curved beam model of the proximal femur for estimating stress using dual-energy X-ray absorptiometry derived structural geometry. J Orthop Res. 1996;14(3):483-92.
19. Peacock M, Turner CH, Liu G, Manatunga AK, Timmerman L, Johnston CC Jr. Better discrimination of hip fracture using bone density, geometry and architecture. Osteoporos Int. 1995;5(3):167-73.
20. Yang L, Peel N, Clowes JA, McCloskey EV, Eastell R. Use of DXA-based structural engineering models of the proximal femur to discriminate hip fracture. J Bone Miner Res. 2009;24(1):33-42.
21. Milgrom C, Gildadi M, Simkin A, et al. The area moment of inertia of the tibia: a risk factor for stress fractures. J Biomech. 1989;22(11-12):1243-8.
22. Beck TJ. Extending DXA beyond bone mineral density: understanding hip structure analysis. Curr Osteoporos Rep. 2007;5(2):49-55.
23. Khennane A. Introduction to finite element analysis using MATLAB® and Abaqus. (Group CPT& F, ed.). Boca Raton FL; 2013.
24. Choisne J, Valiadis JM, Travert C, Kolta S, Roux C, Skalli W. Vertebral strength prediction from Bi-Planar dual energy X-ray absorptiometry under anterior compressive force using a finite element model: An in vitro study. J Mech Behav Biomed Mater. 2018;87:190-6.
25. Colombo C, Libonati F, Rinaudo L, Bellazzi M, Ulivieri FM, Vergani L. A new finite element based parameter to predict bone fracture. PLoS One. 2019;14(12):e0225905.
26. Morgan EF, Bayraktar HH, Keaveny TM. Trabecular bone modulus-density relationships depend on anatomic site. J Biomech. 2003;36(7):897-904.
27. Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3-44.
28. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;4(6):368-81.
29. Siris ES, Chen YT, Abbott TA, et al. Bone mineral density thresholds for pharmacological intervention to prevent fractures. Arch Intern Med. 2004;164(10):1108-12.
30. Trémollieres FA, Pouillès JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. J Bone Miner Res. 2010;25(5):1002-9.
31. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg MA. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. J Clin Densitom. 2011;14(3):302-12.
32. Pothuaud L, Barthe N, Krieg M-A, Mehsen N, Carceller P, Hans D. Evaluation of the potential use of trabecular bone score to complement bone mineral density in the diagnosis of osteoporosis: a preliminary spine BMD-matched, case-control study. J Clin Densitom. 2009;12(2):170-6.

33. McClung MR, Lippuner K, Brandi ML, et al. Effect of denosumab on trabecular bone score in postmenopausal women with osteoporosis. Osteoporos Int. 2017;28(10):2967-73.
34. Lobos S, Cooke A, Simonett G, Ho C, Boyd SK, Edwards WB. Trabecular bone score at the distal femur and proximal tibia in individuals with spinal cord injury. J Clin Densitom. 2019;22(2):249-56.
35. White R, Krueger D, De Guio F, et al. An exploratory study of the Texture Research Investigational Platform (TRIP) to evaluate bone texture score of distal femur DXA Scans - A TBS-based approach. J Clin Densitom. 2021;24(1):112-7.
36. Brianza SZ, D'Amelio P, Pugno N, Delise M, Bignardi C, Isaia G. Allometric scaling and biomechanical behavior of the bone tissue: An experimental intraspecific investigation. Bone. 2007;40(6):1635-42.
37. Taylor ME, Tanner KE, Freeman MAR, Yettram AL. Stress and strain distribution within the intact femur: compression or bending? Med Eng Phys. 1996;18(2):122-31.
38. Ha YC, Yoo JI, Yoo J, Park KS. Effects of hip structure analysis variables on hip fracture: a propensity score matching study. J Clin Med. 2019;8(10):1507.
39. LaCroix AZ, Beck TJ, Cauley JA, et al. Hip structural geometry and incidence of hip fracture in postmenopausal women: what does it add to conventional bone mineral density? Osteoporos Int. 2010;21(6):919-29.
40. Yang L, Palermo L, Black DM, Eastell R. Prediction of incident hip fracture with the estimated femoral strength by finite element analysis of DXA Scans in the study of osteoporotic fractures. J Bone Miner Res. 2014;29(12):2594-600.
41. Tecnologie Avanzate - Bone Strain Index. Available at: https://tecnologieavanzate.com/en/research-and-development/bone-strain-index/.
42. Han KS, Rohlmann A, Zander T, Taylor WR. Lumbar spinal loads vary with body height and weight. Med Eng Phys. 2013;35(7):969-77.
43. Terzini M, Aldieri A, Rinaudo L, Osella G, Audenino AL, Bignardi C. Improving the hip fracture risk prediction through 2D finite element models from DXA images: validation against 3D models. Front Bioeng Biotechnol. 2019;7:220.
44. Ulivieri FM, Piodi LP, Grossi E, et al. The role of carboxy-terminal cross-linking telopeptide of type I collagen, dual X-ray absorptiometry bone strain and Romberg test in a new osteoporotic fracture risk evaluation: A proposal from an observational study. PLoS One. 2018;13(1):e0190477.
45. Ulivieri FM, Piodi LP, Rinaudo L, Scanagatta P, Cesana BM. Bone strain index in the prediction of vertebral fragility refracture. Eur Radiol Exp. 2020;4(1):23.
46. Messina C, Rinaudo L, Cesana BM, et al. Prediction of osteoporotic fragility re-fracture with lumbar spine DXA-based derived bone strain index: a multicenter validation study. Osteoporos Int. 2021;32(1):85-91.
47. Ulivieri FM, Rinaudo L, Piodi LP, et al. Usefulness of dual X-ray absorptiometry-derived bone geometry and structural indexes in mastocytosis. Calcif Tissue Int. 2020;107(6):551-8.
48. Compston J, Cooper A, Cooper C, et al; National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43.
49. Messina C, Piodi LP, Rinaudo L, et al. Bone strain index reproducibility and soft tissue thickness influence: a dual X-ray photon absorptiometry phantom study. Eur Radiol Exp. 2019;3(1):33.
50. Messina C, Acquasanta M, Rinaudo L, et al. Short-term precision error of Bone Strain Index, a new DXA-based finite element analysis software for hip strength assessment. J Clin Densitom. 2021;24(2):330-7.
51. Messina C, Piodi LP, Rinaudo L, et al. Reproducibility of DXA-based bone strain index and the influence of body mass: an in vivo study. Radiol Med. 2020;125(3):313-8.
52. Le NT, Robinson J, Lewis SJ. Obese patients and radiography literature: what do we know about a big issue? J Med Radiat Sci. 2015;62(2):132-41.
53. Messina C, Piodi LP, Grossi E, et al. Artificial neural network analysis of bone quality DXA parameters response to teriparatide in fractured osteoporotic patients. PLoS One. 2020;15(3):e0229820.

Declarations: *There was no funding for this study.*
LR, formerly of the Politecnico of Turin and employed at the commercial company "TECHNOLOGIC S.r.l", is now in charge of Bone Strain Index Project Management for "Tecnologie Avanzate S.r.l."
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