Not only stiffness, but also yield strength of the trabecular structure determined by non-linear μFE is best predicted by bone volume fraction and fabric tensor

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Abstract

The micro-architecture of cancellous bone is considered a major determinant of the fracture risk. Yet, if morphometry tells about alterations of the trabecular network, its elastic behaviour is best described by bone volume fraction (BV/TV) and the fabric tensor, which gives the anisotropy of the trabecular structure. This remains to be proven for yield strength, the onset of bone failure. The microstructure of 126 samples extracted from femoral heads of two female subjects was evaluated on micro-computed tomography scans via 25 structural indices. Parameters such as plate and rod decomposition via ITS and textural analyses by ISV, similar to the trabecular bone score, were also examined. The degree of collinearity between indices was assessed. The indices considered sufficiently independent were included in multi-linear regression models predicting stiffness or yield strength measured via nonlinear micro finite element analyses. The models' accuracy was checked and the contributions of all explanatory variables to the prediction were compared. Our results show that BV/TV alone explained most of the predicted yield strength (76%) and stiffness (89%). BV/TV together with the fabric tensor explained more than 98% of both measures! The fabric tensor also had a larger impact on yield strength (23%) than on the stiffness predictions (9%). On the other hand, the predictive value of the other independent factors (Tb.Th.SD, Tb.Sp.SD, rTb.Th, RR.Junc.D, ISV) was negligible (<1%). In conclusion, just as stiffness, yield strength of femoral trabecular bone is also best explained by BV/TV and trabecular anisotropy, the latter being even more relevant in its post-elastic behaviour.

Keywords: nonlinear μFE; yield properties; trabecular structure; fabric tensor; trabecular bone score; individual trabeculae segmentation

1. Introduction

Osteoporosis disrupts bone remodelling and is partly responsible for the high fracture incidence at the wrist, spine and hip (Cummings and Melton 2002). In particular, the structural integrity of the trabecular bone reduces due to the progressive thinning of the trabeculae and loss of connectivity. Numerous indices derived from bone morphometry (Dempster et al. 2013) were therefore developed to capture specific aspects of the trabecular architecture from micro-computed tomography (μCT) (Hildebrand et al. 1999). The fabric tensor, for instance, describes its overall orientation distribution (Cowin 1986), while the individual trabecula segmentation (ITS) focuses on the discretization between plate-like and rod-like trabeculae (Zhou et al. 2014).

To a large extent, morphological indices are redundant (Hildebrand et al. 1999) and their intrinsic value needs to be evaluated. As those metrics can be retrieved *in vivo* from high-resolution peripheral quantitative CT (HR-pQCT) (Zhou et al. 2014) or simply estimated from dual energy X-ray absorptiometry (DXA) via textural analyses (Pothuaud et al. 2008), their ability to refine fracture risk assessment constitutes a frequent evaluation criterion. However, the risk of fracture is not as deterministic as bone mechanics since it largely depends on random events leading to falls.

Accordingly, we recently proposed to compare most of the existing morphological parameters on a mechanical basis and chose trabecular stiffness as a point of comparison (Maquer et al. 2015). Against popular belief, we showed that bone volume fraction and anisotropy are the best determinants of the elastic properties of human trabecular samples assessed via micro-finite element (μFE) analyses (Maquer et al. 2015). Yet, the failure mechanisms of trabecular bone are complex and results pertaining to its elasticity may not be true for its yield properties.

The aim of the present study is to determine whether the superior predictive value of bone volume fraction and anisotropy holds for yield strength, the onset of bone failure, using validated nonlinear μFE modelling. Additionally, the relative contributions of these two metrics to stiffness and yield strength will be compared.

2. Materials and methods

2.1. Morphological indices

An overview of the study is given in Fig. 1. μCT and μFE data of 126 cubic biopsies were re-analysed (Panyasantisuk et al. 2015a, 2015b). Those samples (5.3 mm side length) were extracted from three femoral heads (two female donors; 66±8 years) and scanned (μCT40, SCANCO Medical, Switzerland). The images were coarsened from 18 to 36 μm voxel size. Bone volume fraction (BV/TV), structure model index (SMI), connectivity density (Conn.D), bone surface (BS), trabecular thickness (Tb.Th, Tb.Th.SD) and spacing (Tb.Sp, Tb.Sp.SD) were evaluated via BoneJ (Doube et al. 2010).

Plate (p, P) and rod (r, R) parameters: pBV/TV, rBV/TV, axial BV/TV (aBV/TV), tissue fraction (pBV/BV, rBV/BV), connection densities (PP Junc.D, RR Junc.D, PR Junc.D), plate surface (Tb.S), rod length (rTb.l), trabecular numbers (pTb.N, rTb.N) and thicknesses (pTb.Th, rTb.Th) were provided by ITS software of the Columbia University (http://innovation.columbia.edu/technologies/m05-076_3d-individual-trabecula-segmentation-its-morphological-analysis-and-modeling-technique).

The anisotropy of the samples was measured via mean intercept length and was represented by a fabric tensor (Cowin 1986) that was normalized into a dimensionless positive definite second-order tensor (Zysset and Curnier 1995):

$$\mathbf{M} = \sum_{\mathrm{i}=1}^{3} m_i(\mathbf{m_i} \otimes \mathbf{m_i}), where\ i = 1, 2, 3 \qquad (1)$$

This fabric tensor describes the three-dimensional arrangement of the trabecular structure. Its spectral decomposition is characterized by three eigenvectors ($\mathbf{m_1}$, $\mathbf{m_2}$, $\mathbf{m_3}$) representing the main directions of anisotropy and three eigenvalues ($m_1 < m_2 < m_3$) representing the magnitude of anisotropy along the corresponding eigenvectors. In particular, the degree of anisotropy (DA) of the samples is calculated as the ratio of the largest and the smallest eigenvalues.

Based on the original description of the trabecular bone score (TBS), the initial slope of the variogram (ISV) reflects the heterogeneity of a planar image by computing the relative change of intensity between neighbouring pixels (Maquer et al. 2016). ISV_x, ISV_y, ISV_z were computed on projections of the μCT reconstructions along x, y and z-axes.

2.2. Numerical testing

μCT voxels were automatically converted to hexahedral finite elements. Trabecular tissue was simulated by an elasto-plastic material law validated against destructive in vitro test of trabecular biopsies cored from femoral neck, distal radius and lumbar vertebrae (Schwiedrzik et al. 2015). Briefly, 21 biopsies excised from 11 donors were scanned by μCT (μCT 40, SCANCO Medical AG, Switzerland). Using a servo-hydraulic testing device (Mini-Bionix, MTS, USA), 10 were compressed quasi-statically and under wet conditions until failure was reached. The top and bottom of the remaining 11 biopsies were embedded in polyurethane to be gripped and tested under the same conditions in tension. The in vitro tests were reproduced via the parallel version of FEAP (ParFEAP 8.3) (Taylor and Govindjee 2013) using μCT-based μFE models and the elasto-plastic material law used in this study. Two parameter sets were tested: Set 1) 0.33% tensile yield strain and 0.81% compressive yield strain (Bayraktar et al. 2004); and Set 2) 0.54% tensile yield strain and 0.81% compressive yield strain (Zysset 1994). Set 2 ensured the best correspondence with the experiments.

Based on this prior work, each element was assigned isotropic elastic properties (Young modulus of 10GPa and Poisson ratio of 0.3), while an approximated Drucker-Prager criterion accounted for the asymmetric yield behaviour of the bone tissue (0.54% tensile yield strain and 0.81% compressive yield strain). Displacement-controlled scenarios were chosen to load our samples using large deformation formulation as detailed elsewhere (Panyasantisuk et al. 2015a, 2015b). Kinematic uniform boundary conditions were prescribed via displacements u on each position x of the sample's boundary Γ: $u(x) = \boldsymbol{\varepsilon}\, x, \forall x \in \Gamma$ and with $\boldsymbol{\varepsilon}$ being the applied strain tensor. Three shear, three tensile and three compressive tests were thus performed up to 2% nominal strain via ParFEAP 8.3. Apparent elastic and yield properties of each sample were computed based on the slope of the normalized stress-strain curves and using a 0.2% strain offset criterion.

2.3. Relationship between morphological indices, stiffness and yield strength

The idea of the study is to determine all the morphological indices that can improve the prediction of the mechanical properties of the trabecular structure. First, those indices were successively included in isotropic and anisotropic regression models inspired by the Zysset-Curnier relationship (Panyasantisuk et al. 2015a, 2015b) to determine the best single predictor. Isotropic models were exclusively based on the variable of interest replacing BV/TV in the relationship, while anisotropic models also considered the eigenvectors and eigenvalues of the fabric tensor. Multi-linear problems created after log transformations of those relationships were solved in order to approximate the elastic and yield properties. Adjusted coefficient of determination (R^2_{adj}) and residual standard error (RSE) were used to quantify the contribution of each structural variable. Unlike the regular coefficient of determination (R^2), R^2_{adj} accounts for the number of explanatory variables (p) in the multi-linear model relative to the sample size (n). R^2_{adj} increases only if the increase in R^2 is more than expected by chance, i.e. if a new explanatory variable really improves the description of the variance of the dependent variable given by the model (Kvålseth 1985). RSE is as well a measure of the goodness of fit. It tells us how strongly the observed values (y_i) vary around the fitted ones ($\hat{y}_i$). Those parameters are computed as follows:

$$R^2_{adj} = 1 - \frac{(1 - R^2)(n - 1)}{(n - p - 1)} \quad (2)$$

$$RSE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n - p}} \quad (3)$$

Still, even after determining the best predictor of the mechanical behaviour of cancellous bone, it remained unclear whether adding other morphological indices along to the best predictor can improve the model. Thus, in a second step, the "global model" was generated by including: 1) the single best predictor, 3) the fabric tensor and 3) all the other morphological indices that were shown to be independent (Fig. 1). The rationale behind the independency was to generate the most accurate model while avoiding collinearity resulting in an overestimation of the regression coefficients due to correlation between explanatory variables. The independent indices were detected via stepwise backward selection based on the variance inflation factor (VIF) (Zuur et al. 2010), which indicates how much a specific variable contributes to the standard error of the regression model. Those with the highest VIF values, except the best predictor, were successively eliminated until only variables with VIF<4 remained and were considered independent. The investigation was conducted in R (3.0.1, *car* package). Finally, an analysis of variance (ANOVA) provided the contribution of each morphological variable included in the global model as percentage of the prediction of elastic and yield properties.

3. Results

The ranges of BV/TV, fabric eigenvalues, degree of anisotropy and computed stiffness and yield strength of our samples were broad (Table 1). The predictive power of the morphometric variables is presented in Table 2. The models represented consistently better stiffness than yield strength. Replacing each morphological index in the isotropic models confirmed that BV/TV is the best single determinant of both stiffness (R^2_{adj} = 0.895, RSE =

0.254 MPa) and yield strength (R^2_{adj} = 0.755, RSE = 0.291 MPa) of trabecular bone.

Anisotropy models always showed a higher predictive value than the isotropic ones. This is particularly striking when the fabric tensor is included along BV/TV, with improvements seen in stiffness (R^2_{adj} = 0.985 i.e. +10% improvement compared to isotropic model and RSE = 0.097 MPa, i.e. -62% error compared to isotropic model) and yield strength predictions (R^2_{adj} = 0.984 i.e. +30% improvement, RSE = 0.074 MPa i.e. -75% error). In other words, BV/TV alone describes 89% and 75% of the variance of stiffness and yield strength, but BV/TV and fabric tensor describe together more than 98% of the variance of both measures!

In its quality of best predictor, BV/TV (VIF = 3.8) was included in the global model together with the fabric tensor (VIF = 1.0) and the other morphological indices that were found independent: Tb.Th.SD (VIF = 3.6), Tb.Sp.SD (VIF = 2.1), rTb.Th (VIF = 1.4), RRJunc.D (VIF = 2.8), ISV_x (VIF = 1.5), ISV_y (VIF = 2.0) and ISV_z (VIF = 3.4). As shown in Fig. 2, BV/TV contributed to 89% and 76% of the stiffness and yield strength predicted by the global model. The trabecular anisotropy given by the fabric tensor contributed less to the predictions of stiffness (9%) than to those of yield strength (23%). The added value of Tb.Th.SD, Tb.Sp.SD, rTb.Th, RRJunc.D, ISVx, ISVy and ISVz to the global model was, however, negligible (<0.5%) (Fig. 2).

4. Discussion

We know for more than 100 years that bone remodelling aligns the trabeculae along the principal stress directions, so the strong relationship existing between fabric and elasticity tensors is not surprising (Cowin 1986). There is also ample evidence that the uni- and multi-axial yield properties of trabecular samples are captured by fabric-based criteria (Wolfram et al. 2012). This study rests on the rigorous statistical analysis of a large panel of morphological parameters, including the fabric tensor. The latter describes the three-dimensional trabecular arrangement, whereas the question of anisotropy is often addressed by simply tilting the main trabecular axis (Bevill et al. 2009a) or via the simplistic degree of anisotropy. The results confirm the superior value of BV/TV and fabric tensor in terms of stiffness prediction, but also demonstrate that both variables are the best determinants of yield strength as well. Accounting for the plate- or rod-like shape of the trabeculae did not improve the stiffness and yield strength predictions of the BV/TV-fabric tensor models.

4.1. The relevance of the morphological indices

The value of indices other than BV/TV and fabric tensor is not denied. In fact, some metrics were found solid determinants of stiffness and yield strength. Simply, many were redundant and were thus excluded from the global model by the VIF selection. There is no consensus regarding the cut-off value below which factors can be safely considered unrelated, even if VIF<10 is a common choice (Zuur et al. 2010). With a stricter criterion (VIF<4), we minimized multi-collinearity among the variables remaining in the global model (BV/TV, fabric, Tb.Th.SD, Tb.Sp.SD, rTb.Th, RRJunc.D and ISV), though only fabric tensor seems to be truly independent from BV/TV (VIF=1). The remaining variables other than BV/TV and anisotropy had minor influence on the predictions. Morphological metrics are therefore either poor surrogate for the mechanical properties of trabecular bone (such as ISV, an ersatz of trabecular bone score (Maquer et al. 2016)) or too strongly related to BV/TV to provide any additional information (e.g. SMI (Hildebrand et al. 1999) and pBV/TV (Zhou et al. 2014). Our findings show that the fabric tensor more largely contributes in explaining the variance of yield strength than it does for stiffness. The elastic constants reflect the asymptotic stiffness of the trabecular structure for very small deformations. Its overall yielding, however, involves small deformations of axial trabeculae, but also large bending deformations of thinner transverse trabeculae (Bevill et al. 2006) and is therefore more sensitive to their orientation distribution (Matsuura et al. 2008).

4.2. Strengths of the study

Unlike our prior work limited to elasticity (Maquer et al. 2015), this study relied on fully nonlinear μFE analyses. Local large deformations such as bending of the trabeculae and the nonlinear material behaviour of bone tissue were accounted for. In particular, tissue-level yielding was simulated by an elasto-plastic material law validated against tensile and compressive tests of trabecular biopsies (Schwiedrzik et al. 2015). While not novel per se, nonlinear μFE modelling was necessary to establish compressive, tensile and shear properties of the same biopsy, as this is only possible numerically. To ease the statistical treatment, however, multi-axial cases were not included in this study. Thanks to its high reproducibility, the technique enabled the testing of a large cohort of 126 specimens. Finally, to check if the results of the nonlinear μFE models were reliable, Panyasantisuk et al. (2015b) compared the yield properties obtained numerically from our samples against those obtained experimentally on other specimens in another study (Wolfram et al. 2012). All yield parameters showed a very good match if the samples were in the same BV/TV range.

4.3. Further considerations

A notable difference with our previous work (Maquer et al. 2015) is the sole use of samples cored from femoral heads of two female donors. Nevertheless, the architecture and stiffness of the samples obtained from these two donors were broadly distributed and consistent with previous studies using samples extracted from femurs, radii, vertebrae and patellae (Gross et al. 2013, Panyasantisuk et al. 2015a, Latypova et al. 2016). The superior value of BV/TV and anisotropy for predicting stiffness hardly depends on density range, anatomical site, or gender (Maquer et al. 2015). We can therefore reasonably speculate that our findings would hold for other anatomical sites and gender, but the final demonstration requires further simulations.

Although the study accounted for 25 structural indices, the new ellipsoid factor (Salmon et al. 2015) was not included. This index essentially provides plate and rod measures, which is an aspect that was largely explored via 14 ITS indices.

Other considerations are related to our modelling choices. Although the µFE models were produced from µCT images coarsened to 36 µm voxel size, reliable estimates of strength can be achieved with voxel sizes up to 80 µm (Bevill et al. 2009b). Another point is that our material law was validated against tensile and compressive tests, but not against shear (Schwiedrzik et al. 2015), which is still better than deriving shear strength from a model only validated under compression (Sanyal et al. 2012). Finally, the µFE technique overlooks the fact that trabecular bone tissue is heterogeneous. For some authors, assuming otherwise leads to an overestimation of the trabecular stiffness (Blanchard et al. 2013). Yet in fact, mineral heterogeneity has a minor influence on the trabecular stiffness (Gross et al. 2012). In reality, trabecular tissue is also anisotropic. Tensor tomography can quantify this anisotropy via 3D reconstructions of the mineralized fibrils, but for single trabeculae only (Liebi et al. 2015). On the other hand, modelling the trabecular tissue isotropic actually induces little to no error in the µFE results (Cowin 1997). More important, perhaps, is the accumulation of tissue microdamage that significantly reduces trabecular stiffness and strength (Hernandez et al. 2014). Those microcracks are not captured by µCT and are thus not accounted for by our µFE models. Aspects such as altered composition, lamellar organization, and pre-existing microcracks may need to be considered in future studies, but assuming homogenous isotropic properties has at least the advantage of uncoupling tissue-level from structural considerations (the latest being our focus).

4.4. Conclusions

Despite few shortcomings, this study showed that stiffness and yield strength of femoral trabecular samples are best predicted by BV/TV and fabric tensor. Although stiffness and yield strength are highly correlated, this is the first time that such result is demonstrated for tensile, compressive and shear load cases and for a large dataset. Other architectural indices depict the trabecular structure, but have in fact limited value in terms of mechanical predictions, if trabecular density and anisotropy can be measured. While homogenised finite element models often discard the anisotropy of trabecular bone, it clearly seems that its role in the failure behaviour of trabecular bone is underestimated.

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Tables

Table 1. The ranges of bone volume fraction (BV/TV), eigenvalues of the fabric tensor (m_1, m_2, m_3), degree of anisotropy (DA=m_3/m_1), computed elastic (E) and shear (G) moduli and computed yield strengths in tension (σ^+), compression (σ^-) and shear (σ^s) of our samples were broad. x, y, z indicates the loading directions.

		Mean ± SD	**Min**	**Max**
Morphology				
	BV/TV	0.27 ± 0.08	0.12	0.40
	m_1	0.80 ± 0.05	0.66	0.92
	m_2	0.94 ± 0.05	0.84	1.07
	m_3	1.25 ± 0.07	1.06	1.45
	DA	1.57 ± 0.18	1.17	2.14
Stiffness [MPa]				
Elastic moduli	E_x	634.67 ± 323.45	97.01	1445.30
	E_y	886.28 ± 459.12	216.15	2012.62
	E_z	1370.12 ± 640.10	382.48	2972.61
Shear moduli	G_{xy}	272.91 ± 140.86	52.96	606.33
	G_{xz}	326.69 ± 166.52	75.64	721.15
	G_{yz}	430.50 ± 210.06	118.67	860.12
Yield Strength [MPa]				
Tension	σ^+_x	3.91 ± 1.70	1.00	7.64
	σ^+_y	5.57 ± 2.46	1.52	10.90
	σ^+_z	8.21 ± 3.22	2.46	15.83
Compression	σ^-_x	6.05 ± 2.78	1.44	12.34
	σ^-_y	8.57 ± 3.99	2.18	17.43
	σ^-_z	12.72 ± 5.21	3.59	25.05
Shear	σ^s_{xy}	5.09 ± 2.25	1.42	9.81
	σ^s_{xz}	5.88 ± 2.46	1.62	11.03
	σ^s_{yz}	7.51 ± 3.04	2.01	13.12

Table 2. Adjusted coefficient of determination (R^2_{adj}) and residual standard error (RSE [MPa]) show that BV/TV, alone or with fabric tensor, is the best single predictor of stiffness and yield strength. Including the fabric tensor always improved the models.

		Stiffness		Yield strength	
		Isotropic model	*Anisotropic model*	*Isotropic model*	*Anisotropic model*
STANDARD					
BV/TV	R^2_{adj}	**0.895**	**0.985**	**0.755**	**0.984**
	RSE	**0.254**	**0.097**	**0.291**	**0.074**
Conn.D	R^2_{adj}	0.559	0.646	0.200	0.425
	RSE	0.521	0.467	0.527	0.447
SMI	R^2_{adj}	0.849	0.939	0.683	0.913
	RSE	0.305	0.194	0.332	0.174
Tb.Th	R^2_{adj}	0.786	0.880	0.582	0.817
	RSE	0.363	0.272	0.381	0.252
Tb.Sp	R^2_{adj}	0.785	0.872	0.57	0.796
	RSE	0.364	0.281	0.386	0.266
BS	R^2_{adj}	0.878	0.969	0.727	0.958
	RSE	0.274	0.138	0.308	0.121
Tb.Th.SD	R^2_{adj}	0.633	0.729	0.334	0.572
	RSE	0.476	0.409	0.481	0.385
Tb.Sp.SD	R^2_{adj}	0.640	0.731	0.334	0.565
	RSE	0.471	0.407	0.481	0.388
ITS					
pBV/TV	R^2_{adj}	0.889	0.981	0.748	0.980
	RSE	0.261	0.108	0.296	0.084
rBV/TV	R^2_{adj}	0.493	0.584	0.095	0.327
	RSE	0.559	0.506	0.560	0.483
aBV/TV	R^2_{adj}	0.858	0.954	0.697	0.936
	RSE	0.296	0.169	0.324	0.149
pBV/BV	R^2_{adj}	0.759	0.858	0.539	0.782
	RSE	0.385	0.296	0.400	0.275
rBV/BV	R^2_{adj}	0.750	0.849	0.525	0.768
	RSE	0.393	0.306	0.406	0.284
pTb.N	R^2_{adj}	0.757	0.842	0.523	0.745
	RSE	0.387	0.312	0.407	0.298
rTb.N	R^2_{adj}	0.508	0.597	0.118	0.346
	RSE	0.551	0.499	0.553	0.476
pTb.Th	R^2_{adj}	0.773	0.867	0.561	0.797
	RSE	0.374	0.286	0.39	0.266
rTb.Th	R^2_{adj}	0.518	0.608	0.138	0.368
	RSE	0.545	0.492	0.547	0.468
pTb.S	R^2_{adj}	0.558	0.656	0.208	0.450
	RSE	0.522	0.461	0.524	0.437
rTb.l	R^2_{adj}	0.767	0.854	0.542	0.766
	RSE	0.379	0.300	0.398	0.285
RRJunc.D	R^2_{adj}	0.513	0.608	0.131	0.369
	RSE	0.548	0.492	0.549	0.468
RPJunc.D	R^2_{adj}	0.570	0.656	0.218	0.440
	RSE	0.515	0.461	0.521	0.441
PPJunc.D	R^2_{adj}	0.715	0.799	0.454	0.674
	RSE	0.419	0.352	0.435	0.336
TBS SURROGATE					
ISV_x	R^2_{adj}	0.514	0.605	0.133	0.363
	RSE	0.547	0.494	0.548	0.470
ISV_y	R^2_{adj}	0.591	0.686	0.264	0.502
	RSE	0.502	0.440	0.505	0.416
ISV_z	R^2_{adj}	0.625	0.724	0.318	0.562
	RSE	0.481	0.413	0.487	0.390

Figure captions

Fig. 1. (1) 126 cubic trabecular samples were cropped from the μCT reconstructions of femoral heads. (2) 25 morphological indices were evaluated for each cube and used to predict stiffness and yield tensors computed from μFE (3) via three regression models. (4) The isotropic model is based on a single variable. In addition to the single variable, the anisotropic model accounts for the anisotropy of the sample given by their fabric tensor. With these two models, we determine the best predictor for stiffness and yield strength. Yet, as it is still not sure whether the model's predictions can be further improved by adding extra indices along, a third model is proposed. This "global" model is a combination of the best predictor, fabric tensor and all the indices considered independent.

Fig. 2. The relative contribution of each variable in the global model. Bone volume fraction (BV/TV) and fabric tensor explain most of the stiffness and yield properties of the trabecular bone. The contribution of the other independent indices (i.e. Tb.Th.SD, Tb.Sp.SD, rTb.Th, RR.Junc.D and ISV) is negligible.