

# Clinical interest of bone texture analysis in osteoporosis: a case control multicenter study

E. Lespessailles · C. Gadois · I. Kousignian ·  
J. P. Neveu · P. Fardellone · S. Kolta · C. Roux ·  
J. P. Do-Huu · C. L. Benhamou

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## Abstract

**Summary** We demonstrate the clinical interest of bone texture analysis with a new high resolution X-ray device. We have found that the combination of BMD and texture parameter values provided a better assessment of the fracture risk than that obtainable solely by BMD measurement.

**Introduction** Osteoporosis is characterized by BMD and trabecular bone microarchitecture. We have developed a new high-resolution X-ray device with direct digitization. The aim of this study was to demonstrate in a multicenter case control study the clinical interest of bone texture analysis with this new device.

**Methods** In this cross-sectional multicenter case-control population study in post-menopausal women, 159 osteoporotic fractures were compared with 219 control cases. Images were obtained on calcaneus with a direct digital X-ray device (BMA™, D3A Medical Systems). Co-occurrence, run-length matrices and the fractal parameter Hmean were evaluated. BMD was measured at the lumbar spine (LS), femoral neck (FN) and total hip (TH) by DXA.

**Results** The three texture parameters were significantly lower in osteoporotic fracture cases than in control cases. These differences persisted after adjustment for TH BMD. Receiver operating characteristic curves were used to compare the discriminant capacity of texture parameters and BMD measurements for fracture. The highest areas under curve (AUC) were 0.721 for TH BMD and 0.706 for Hmean (AUC THBMD vs. AUC Hmean,  $p = \text{NS}$ ). We determined the threshold between high and low Hmean parameter values and then the odds ratios (OR) of fracture for low Hmean, for BMD  $\leq 2.5$  SD in the T-score and for combinations of both parameters. The OR of fracture for low H was 2.72 (95% CI, 1.36–5.4). For a FN BMD  $\leq -2.5$  SD, the OR of 4.78 (2.19–10.43) shifted to 14.06 (4.41–44.85) adding H.

**Conclusions** These data confirmed the clinical interest of the combination of BMD and texture parameters to improve the assessment of the risk of fracture other than obtainable by the sole BMD measurement.

E. Lespessailles (✉) · C. Gadois · C. L. Benhamou  
Ipros - Service de Rhumatologie CHR d'Orléans,  
Orléans, France  
e-mail: eric.lespessailles@chr-orleans.fr

J. P. Do-Huu  
D3A Medical Systems Orleans,  
Orléans, France

I. Kousignian  
INSERM CIC 202,  
Tours, France

I. Kousignian  
Université François-Rabelais de Tours,  
Tours, France

S. Kolta · C. Roux  
Service de Rhumatologie, Hôpital Cochin,  
Paris, France

J. P. Neveu · P. Fardellone  
Département de Rhumatologie, Hôpital Nord,  
Amiens, France

P. Fardellone  
Unité Inserm ERI 12,  
Amiens, France

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## Introduction

If the risk of osteoporotic fractures increases with decreasing bone mineral density (BMD), each standard deviation

(SD) decrease in BMD is associated with a 1.5 to 3.0-fold increase in fracture risk [1]. Other fracture risk factors play a role even after adjustment for BMD [2]. In addition, there is a growing body of evidence that many adults without densitometric osteoporosis are at increased risk of fracture and a high percentage of fracture occurs in women with T-score above  $-2.5$  SD [3, 4]. The percentage of non-vertebral fractures, including hip, wrist and upper humerus fractures that occurred in women with osteoporosis, osteopenia or normal BMD T-score, were assessed prospectively in the Rotterdam study [3]. It was found that, respectively, 43.3% and 12.6% of all non-vertebral fractures occurred in women with osteopenia or normal BMD [3]. In the Study of Osteoporotic Fractures, among the 3% of subjects who experienced a hip fracture, 54% had a BMD T-score at the femoral neck above  $-2.5$  SD [4]. In the same study 74% of women with non-spine fractures had a total hip T-score  $>-2.5$  SD [4].

Consequently, methods which can help to identify women with BMD in the osteopenia or normal range who, however, are at risk of fracture should be very useful. We have previously developed and validated a trabecular bone texture analysis on radiographic images [5]. This analysis performed on cadaveric os calcis specimen *ex vivo* correlated with site-matched histomorphometric findings [6] and with biomechanical properties [7]. Furthermore, it has been shown that texture analysis on X-ray radiographic images and 3D by conventional micro CT [8] micro-MRI [9] or by synchrotron micro-CT [10] were correlated.

We have found that our radiographic texture analysis was able to discriminate spine fracture cases from control cases [11]. Finally, in a larger group of postmenopausal women we have demonstrated that this analysis and BMD assessment provided independent and complementary information to separate fracture cases (hip, vertebral and wrist) from control cases [12].

Recently, we have developed a new high resolution X-ray device with direct digitization [13], named the BMA for bone microarchitecture. We have shown that this new digital X-ray device provided a better precision of texture parameters than what was previously found [5] on digitized films [13]. Following this validation, with this cross-sectional study, we have aimed to demonstrate in a multicenter case control study the clinical interest of this texture analysis applied to images obtained on this new device.

## Materials and methods

### Subjects

The study was a multicenter case control study in postmenopausal women. The protocol was approved by

an independent regional ethics committee. The study was made possible by grants from French clinical research hospital program (PHRC). All the patients and control women voluntarily entered the study after written informed consent. They were recruited from three centers (CHU Amiens, CHR Orléans, CHU Cochin Paris) from November 2004 to February 2006. Patients were systematically screened from all women attending the bone densitometry unit for routine clinical care and from patients hospitalized in the rheumatology, orthopaedy and geriatry units. Three hundred and ninety-five women were enrolled in the study as controls. The subjects with wrist and hip fracture were recruited from the orthopaedic surgery unit of the three hospitals. The vertebral fracture cases came from recruitment by the rheumatology and bone densitometry units. All fracture cases were reviewed by experienced investigators who considered the diagnosis of fragility fracture if it occurred after the age of 40 years. The cases were described as either spontaneous fractures, fractures resulting from strenuous activity, fractures after falls from standing height or less (low trauma energy) and following radiologic data. The presence of vertebral fractures was diagnosed, using lateral spine radiographs according to Genant's classification with grade II or more. All the patients (cases and controls) filled out an osteoporosis risk questionnaire that included: age, personal and familial history of fracture, tobacco (yes or no), alcohol (yes or no, number of units per week), menopausal status (time since menopause), use of hormonal replacement therapy (HRT) (yes or no, treatment duration), treatment by oral corticosteroid (yes or no, dose and duration), other medication (tamoxifen, thyroxin, etc.) and other diseases (rheumatoid arthritis, etc.). All these patients were measured for weight, height and the body mass index (BMI). Participants were also asked for the need to use their arms to assist themselves in standing up from a chair and for physical activity (less or more than two hours per week for the following activities: walking, gardening, sport, etc.). We have included in the fracture group post-menopausal women having vertebral fracture, hip fracture and other non-vertebral fractures, excluding fractures having occurred before 40 years and those of the face, fingers, toes, skull and cervical spine. Patients treated with corticosteroids, fluoride, bisphosphonates, HRT, tibolone, calcitonin, SERM, and PTH for more than six months in the last year before inclusion were excluded. We also excluded patients with known diseases which could interfere with bone metabolism: osteomalacia, bone cancer, myeloma, Paget's disease, hyper parathyroidism, hyperthyroidism not treated, severe renal or hepatic insufficiency, prolonged immobilisation (more than two months in the last year before inclusion). For each fracture cases recruited it was recommended in each center to enrol control cases paired for age ( $\pm 5$  years) and BMI ( $\pm 2$  kg/m). Control cases

were excluded in case of treatment or disease which could interfere with bone metabolism.

We enrolled 149 osteoporotic fractures cases and 395 control cases. There were 46 vertebral fractures, 31 hip fractures, 33 wrist fractures, and 39 other fractures (five elbow, five arm, six rib, one tibia, two metatarsus, six leg, five proximal humerus, and nine ankle fractures). The group studied comprised the 149 fractures cases and 219 control cases matched on age and BMI as indicated above.

Among this group, we then carried out a strict matching for weight ( $\pm 1$  kg) between fracture and control cases as weight and medullar fat might be significant confounding factors in texture parameter assessment [14, 15]. This matching process conducted to a second group of 93 fracture cases and 93 controls. In this second group there were 24 hip fractures, 23 vertebral fractures, 23 wrist fractures and 23 other fractures (elbow, rib, ankle, leg, and humerus). Figure 1 showed the patient disposition in this study.

#### Bone densitometry

BMD was measured using dual-energy X-ray absorptiometry (DXA) (Hologic, Waltham MA, Delphi) at the hip and lumbar spine (LS). The standard analysis procedure of the

hip recommended by the manufacturer was performed on all patients and controls. Total hip (TH), femoral neck (FN) BMD were assessed on the left hip and on the contralateral (non-fractured) femur in case of hip fracture.

#### Microarchitecture quantification

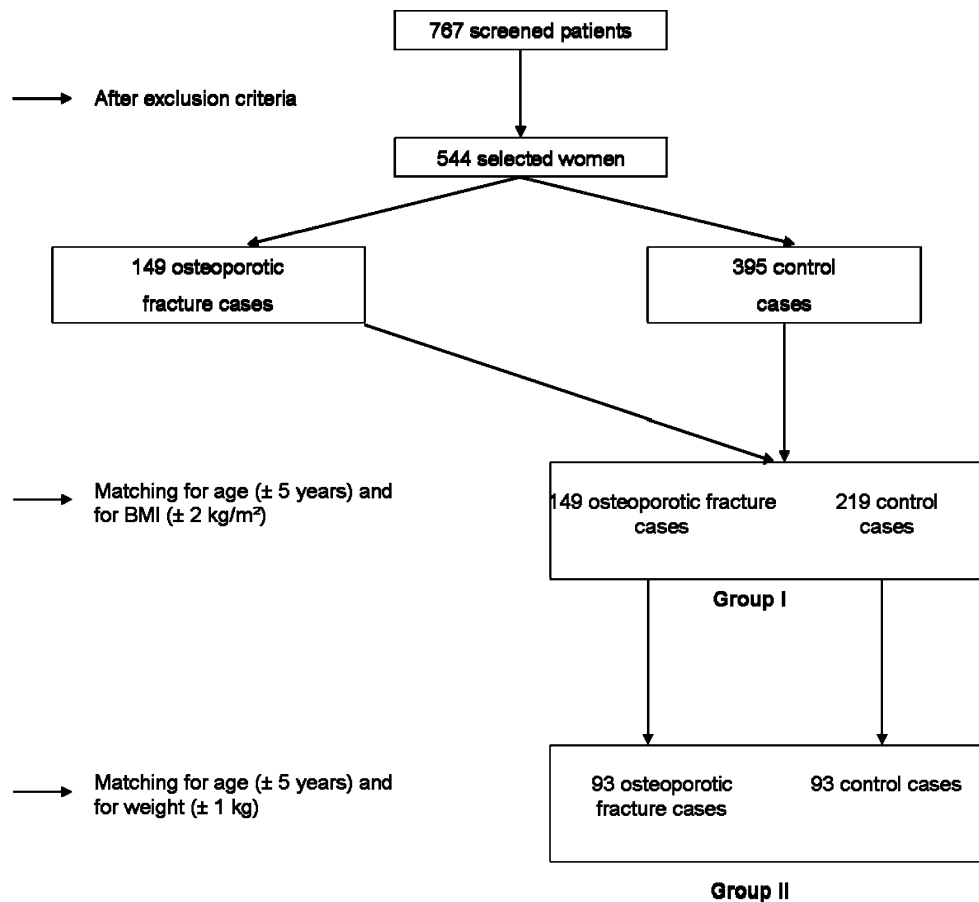
##### Image acquisition

Images were obtained on calcaneus with a direct digital X-ray prototype (BMA<sup>TM</sup>, D3A Medical Systems, Orleans, France). The devices for the multicenter study were cross-calibrated. The cross-calibration procedure has been described elsewhere [13].

During the study, a calibration test was carried out each day of exam using an external phantom to detect any potential drift of the instrumentation. Inter device comparison was performed before the beginning of the study (30 subjects were measured successively on two similar devices). The root mean square coefficient of variation was 0.90; 0.57 and 0.65% for Hmean, run length and co-occurrence, respectively.

The same radiographic parameters were used for the prototypes. Focal distance was settled at 1.15 m. X-ray

**Fig. 1** patient group disposition



parameters were 55 kV and 20 mAs for all patients. Scanning the heel permitted the selection of a similar measurement site (ROI) for each subject by using anatomical landmarks as previously described [5]. These anatomical landmarks were localized by the operator, allowing a positioning of the ROI. These anatomical landmarks are localized by the operator on the image, allowing a positioning of the ROI (1.6×1.6cm) performed by the software device (Fig. 2). Then three texture parameters were calculated on the ROI to evaluate the bone micro-architecture quality.

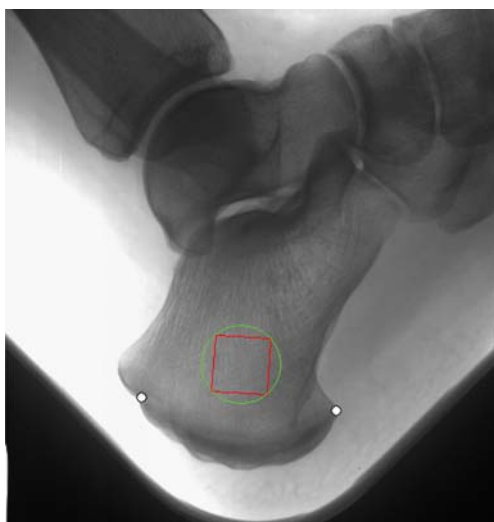
#### Trabecular bone texture parameters

Three parameters were calculated, these parameters have been previously described in details [13]. The Hmean parameter is related to the fractal dimension  $D$  by  $H=2-D$ . The higher  $H$  is, the smaller is the roughness of the texture.

For this study, although many parameters of co-occurrence exist, we have chosen the energy parameter as defined by Haralick [16]. Run length encoding is based on the extraction of texture parameters from the statistical repartition of run. Many run length parameters can be calculated, for this study the short run emphasis parameter has been chosen. Theoretically this last parameter is evolving in an inverse direction as regard to Hmean and co-occurrence; for better understanding purposes we calculated the opposite and expressed the run length by this opposite parameter.

#### Data analysis

To discriminate fracture from the control cases Student's  $t$ -test was used. Analysis of variance and ANCOVA were performed to compare average values of texture parameters



**Fig. 2** ROI for texture analysis at the calcaneus with the two anatomical landmarks

between control and fracture cases with adjustment for age and THBMD when necessary (group I) and with adjustment for TH BMD (group II). All tests were two-sided, and  $p$  values below 0.05 were considered to denote statistical significance.

The discriminant capacity of texture parameters and BMD parameters was assessed by means of receiver operating characteristic (ROC) curves analysis. The area under the ROC curves was calculated and significance level was assessed to compare the area under ROC curves. Correlation analysis between BMD parameters and texture parameters, between texture parameters and age or time since menopause were performed by determining Pearson correlation coefficients and by Spearman's test when the data were not normally distributed.

For the diagnosis of fracture, we calculated the sensitivity and specificity as a function of Hmean. Then we determined the best compromise between sensitivity and specificity by the cross point of the two curves representing sensitivity and specificity. This threshold point was used to estimate the odds ratio (OR) of fractures as a function of two levels of the texture parameters named low and high texture parameter value.

Then we determined the OR by a logistic regression analysis of all fractures according to BMD status normal or osteopenic on one hand (T-Score  $>-2.5$  SD) and OP on the other hand (T-Score  $\leq -2.5$  SD) in terms of LSBMD, FNBMD, THBMD. Then we determined the same OR by adding the high or low texture parameters in patients. Patients with BMD T-Score  $>-2.5$  SD and with high texture parameters were taken as reference.

For analysis of the discriminant ability of the parameters, the odds ratio (OR) was calculated as the exponent of the logistic regression equation coefficient.

Z-score of texture parameters was calculated. With linear regression analysis of the control group, homogeneous SD, an expected value of variable, is calculated due to age. A difference was calculated between the real value and the expected. Then the difference is divided by the standard deviation. Gradient of risk and associated 95% Confidence Interval was calculated for the texture parameters by logistic regression.

All statistical analyses were performed using SAS software package version 9.1 (SAS Institute, Cary, North Carolina, USA).

## Results

In Table 1 are reported the characteristics of the group I (149 fracture cases versus 219 control cases). In spite of age matching, differences in age persisted between fracture cases and controls in this population. The three texture

**Table 1** Comparisons of parameters in the group I matched on age and body mass index (BMI) for fracture cases and control cases

	Fracture cases Mean ± SD* (n=149)	Controls Mean ± SD (n=219)	Statistical Raw	Significance Adjusted for age	p value* Adjusted for age and TH BMD
Age (yr)	72.1±11.3	69.5±9.6	0.02		
Weight (kg)	63.9±13.2	63.5±12.2	NS		
Height (cm)	155.6±7.1	155.8±12.4	NS		
BMI (kg/m)	26.4±5.4	26.1±4.8	NS		
LSBMD (g/cm)	0.838±0.149	0.903±0.153	<0.0001	<0.0001	
FN BMD (g/cm)	0.613±0.114	0.680±0.100	<0.0001	<0.0001	
TH BMD (g/cm)	0.724±0.141	0.808±0.128	<0.0001	<0.0001	
Hmean	0.600±0.035	0.612±0.031	0.004	0.003	0.01
Run-length	2.247±0.068	2.274±0.061	<0.0001	<0.0001	0.0005
Co-occurrence	2.761±0.087	2.799±0.079	0.0001	<0.0001	0.0003

\*: p-values of the comparison between fracture cases and control cases using Student T-test and ANCOVA

parameters were significantly lower in osteoporotic fracture cases than in control cases. These differences persisted after adjustment for age and THBMD.

In Table 2 are reported the characteristics of the group II (93 fracture cases versus 93 control cases). The three texture parameters were significantly lower in fracture cases than in control cases even after adjustment for THBMD.

In Fig. 3, ROC curves of lumbar spine BMD, FNBMD, THBMD, Hmean, run-length and co-occurrence parameters are reported with the areas under curve. There were no statistical differences between the area under curves for THBMD versus Hmean (AUC=0.721 versus 0.706).

Figure 4 and Table 3 described OR of all fractures as a function of BMD values at the lumbar spine, femoral neck and total hip and the Hmean parameter. In the model taking account both BMD and texture parameter values, it could be noticed that adding texture parameters to BMD systematically improved the OR of fracture (cf. Fig. 3). As an example, when LSBMD  $\leq -2.5$  is associated with a high Hmean value, the OR of all fractures was 3.79 [95% CI=1.30–11.04] [p=0.01]. When LSBMD  $\leq -2.5$  was combined with low Hmean value, the OR was 7.23 [2.10–24.87] [p=0.002].

OR of all fractures as a function of BMD values and run-length or co-occurrence parameters consistently showed a higher OR when the texture parameter was added to the BMD values than when each parameter was taken separately (data not shown). Gradient of risk ranged from 1.97 to 6.27 for each 1 SD decrease in parameters (Table 4).

In the control population (n=395 subjects), we found significant relationships between the texture parameters and age or time since menopause (Table 5). Texture parameters were found to be inversely associated with age and time since menopause, all p values between 0.01 and 0.0001.

Texture parameters were independent from BMD parameters whatever the site of measure, all p values were insignificant (Table 5).

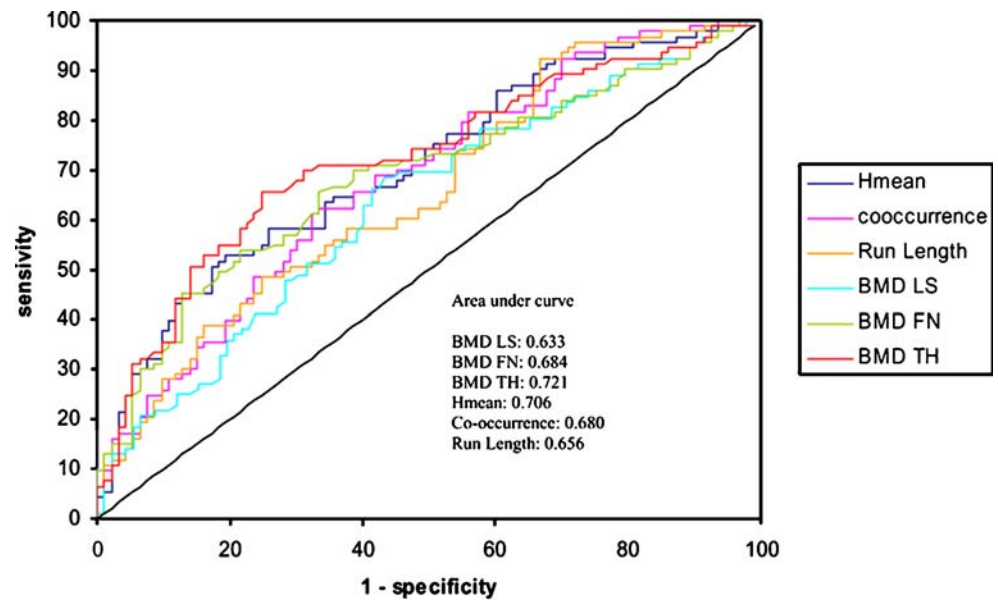
A statistical analysis using ANOVA concerning the results from the three centers has been done in order to detect an effect linked to the clinic site (center effect). There were neither statistical differences for anthropometric parameter nor for texture parameters. We have found a statistical difference only for femoral neck BMD and total hip BMD (p for ANOVA, respectively, 0.0032 and 0.0027). However as proper adjustments for BMD have been

**Table 2** Comparison of parameters in the group II matched on age and weight for fracture cases and control cases

	Fracture cases mean ± SD (n=93)	Controls mean ± SD (n=93)	Statistical raw	p value Adjusted for TH BMD
Age (yr)	71.2±10.6	68.7±9.8	NS	
Weight (kg)	63.2±10.2	63.2±10.0	NS	
Height (cm)	156.4±6.0	157.2±5.9	NS	
BMI (kg/m)	25.9±4.3	25.6±4.1	NS	
LSBMD (g/cm)	0.856±0.148	0.926±0.158	0.022	
FN BMD (g/cm)	0.620±0.113	0.685±0.094	0.02	
TH BMD (g/cm)	0.731±0.137	0.830±0.115	<0.0001	
Hmean	0.601±0.035	0.625±0.028	<0.0001	<0.0001
Run-length	2.246±0.070	2.286±0.063	<0.0001	<0.0001
Co-occurrence	2.758±0.091	2.817±0.079	<0.0001	<0.0001

\*: p-values of the comparison between fracture cases and control cases using Student T-test and ANCOVA

**Fig. 3** Receiver operating characteristic (ROC) curves for LS BMD, TH BMD, FN BMD, Hmean, co-occurrence and run length parameter



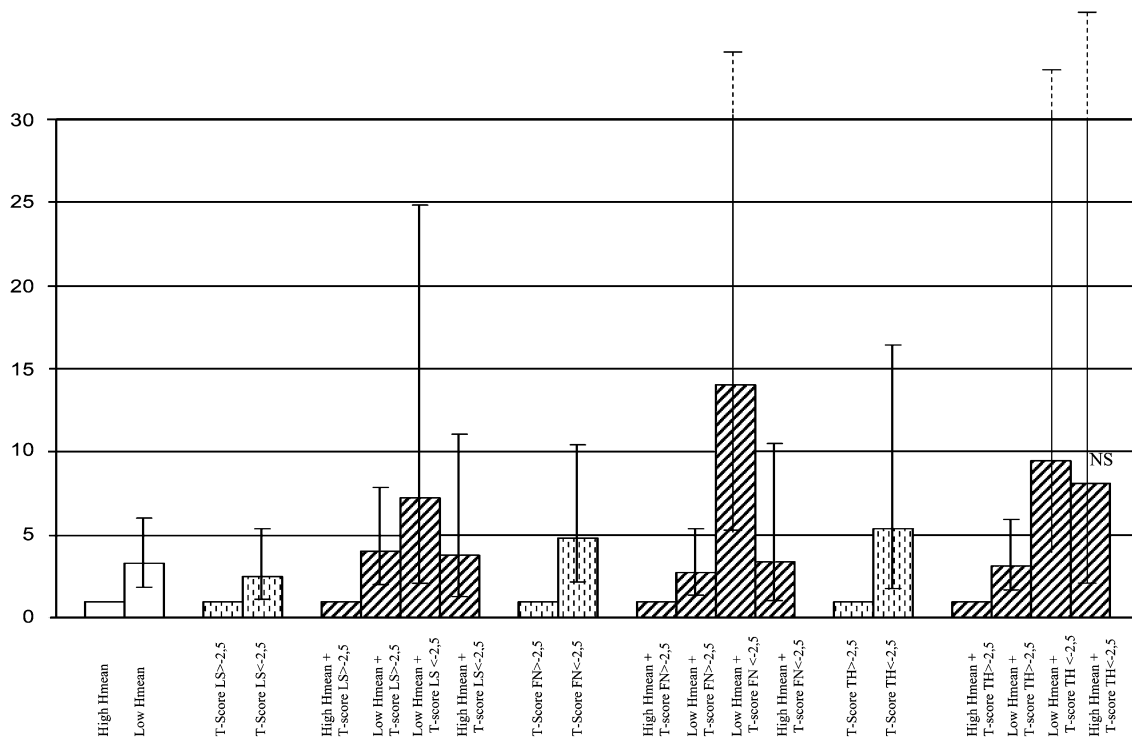
realised, this center effect on BMD doesn't interfere with our results.

The analysis of the fracture cases in sub groups by site of fracture is reported in Table 6.

**Discussion**

This is the first multicenter study in osteoporotic fracture cases showing the clinical interest of bone texture analysis.

Furthermore it was performed with a new device using a direct digitization of the radiologic images. In this study we have shown that even after adjustment for TH BMD the texture parameters permitted to separate fracture cases from controls. We have also confirmed the interest of the fractal parameter Hmean, if we take into account its relationship with the body weight. Indeed, as indicated in the materials and methods section surrounding soft tissues may influence bone texture parameters assessment. In the paper by Vokes et al. [17] body mass index and weight in pound were also



**Fig. 4** Odds ratios [IC 95%] of all fractures as a function of H parameter and BMD values

**Table 3** Odds ratios (OR) and 95% CI values of fractures as a function of Hmean and BMD values

Classes	OR [CI 95%]	p value
High Hmean	1	
Low Hmean	3.31 [1.82–6.03]	0.0001
LS_T-score > -2.5 SD	1	
LS_T-score ≤ -2.5 SD	2.45 [1.12–5.38]	0.03
LS_T-score > -2.5 SD + High Hmean	1	
LS_T-score > -2.5 SD + Low Hmean	3.99 [2.02–7.85]	<0.0001
LS_T-score ≤ -2.5 SD + Low Hmean	7.23 [2.10–24.87]	0.002
LS_T-score ≤ -2.5 SD + High Hmean	3.79 [1.30–11.04]	0.01
FN_T-score > -2.5 SD	1	
FN_T-score ≤ -2.5 SD	4.78 [2.19–10.43]	0.0008
FN_T-score > -2.5 SD + High Hmean	1	
FN_T-score > -2.5 SD + Low Hmean	2.72 [1.36–5.40]	0.004
FN_T-score ≤ -2.5 SD + Low Hmean	14.06 [4.41–44.85]	<0.0001
FN_T-score ≤ -2.5 SD + High Hmean	3.38 [1.08–10.54]	0.04
TH_T-score > -2.5 SD	1	
TH_T-score ≤ -2.5 SD	5.34 [1.73–16.47]	0.004
TH_T-score > -2.5 SD + High Hmean	1	
TH_T-score > -2.5 SD + Low Hmean	3.12 [1.65–5.91]	0.0005
TH_T-score ≤ -2.5 SD + Low Hmean	9.49 [2.53–35.68]	0.0009
TH_T-score ≤ -2.5 SD + High Hmean	8.14 [0.87–76.13]	0.06

CI = confidence interval  
 TH = total hip  
 FN = femoral neck  
 LS = lumbar spine

very similar between fracture and no fracture cases, respectively 27±7 versus 27±6 kg/m<sup>-2</sup> and 148±36 versus 149±30 lbs.

Our study demonstrates that bone texture analysis at the calcaneus provides an assessment of some aspect of bone fragility complementary to the BMD data. We have shown

**Table 4** Z score of Hmean, run length, co-occurrence and TH BMD and gradient of risk (GR) with 95% CI values for all fractures

	Z Score ± SD	GR [CI 95%] (p value)
Hmean	-0.441±1.225	3.38 [1.81–6.32] (p=0.0001)
Run Length	-0.321±1.104	1.97 [1.06–3.64] (p=0.03)
Co-occurrence	-0.375±1.137	2.88 [1.54–5.38] (p=0.0009)
TH BMD	-0.430±1.179	6.27 [3.11–12.65] (p=<0.0001)

**Table 5** Correlation coefficients between age, weight, time since menopause, bone mineral density at the lumbar spine (LS), total hip (TH), femoral neck (FN) and the three texture parameters in the control population (n=395)

	Hmean	Run length	Co-occurrence
<b>Age</b>	<b>-0.21</b>	<b>-0.14</b>	<b>-0.16</b>
p	p<0.0001	0.005	0.002
<b>Weight</b>	<b>0.28</b>	<b>0.40</b>	<b>0.37</b>
p	p<0.0001	p<0.0001	p<0.0001
<b>Height</b>	<b>0.01</b>	<b>0.11</b>	<b>0.11</b>
p	NS	0.02	0.03
<b>Time since menopause</b>	<b>-0.15</b>	<b>-0.13</b>	<b>-0.13</b>
p	0.006	0.01	0.02
<b>TH BMD</b>	<b>0.09</b>	<b>0.07</b>	<b>0.04</b>
p	NS	NS	NS
<b>FN BMD</b>	<b>0.03</b>	<b>0.09</b>	<b>0.07</b>
p	NS	NS	NS
<b>LS BMD</b>	<b>0.06</b>	<b>0.02</b>	<b>0.01</b>
p	NS	NS	NS

that adding one of the three texture parameters to BMD values either at the lumbar spine, the femoral neck or the total hip led to an improvement of the OR of fractures (Fig. 4). These latter data and the fact that texture parameters can differentiate fracture from control cases even after adjustment for BMD confirmed the complementary interest of texture parameters in the prediction of fracture risk. We have demonstrated that a site-matched measurement of BMD and texture parameters at the calcaneus were relatively independent [13]. So, we can assume that the better fracture risk assessment when combining BMD at the lumbar spine and the hip with texture parameters was not the unique result of an assessment at another bone site (the calcaneus), but the assessment of the risk of fracture by another method (trabecular bone texture).

As BMD measurement has a key role both for diagnosis and assessment of the risk of fracture, an interesting method would be to adapt on DXA device texture analysis technique. This idea has been applied by Vokes et al. [17]. In their paper these authors have used a texture analysis performed on calcaneus images obtained using a peripheral densitometer especially equipped to provide high resolution images. They found that texture analysis separated subjects with and without fractures as well as hip BMD. However the instrument they used is a peripheral densitometer and central DXA might not have sufficiently high resolution to permit relevant texture analysis.

We agree with Vokes et al. [17] that bone images do not have simple relationships between log surface area and log pixel size. Thus we do not use a box counting method for fractal analysis [5, 11, 12]. We have developed and

**Table 6** Comparison of parameters in the group II for hip fractures, vertebral fractures and non-vertebral fractures versus control cases

	Hip fracture Mean $\pm$ SD (n=24)	Vertebral fractures Mean $\pm$ SD (n=23)	Non-vertebral fractures Mean $\pm$ SD (n=70)	Controls Mean $\pm$ SD (n=93)
LSBMD (g/cm)	<b>0.849<math>\pm</math>0.145</b>	<b>0.832<math>\pm</math>0.154</b>	<b>0.863<math>\pm</math>0.147</b>	<b>0.926<math>\pm</math>0.158</b>
p	0.04*	0.03*	0.01	
FN BMD (g/cm)	<b>0.523<math>\pm</math>0.079</b>	<b>0.615<math>\pm</math>0.078</b>	<b>0.622<math>\pm</math>0.123</b>	<b>0.685<math>\pm</math>0.094</b>
p	<10 <sup>-4</sup> *	0.006*	0.002	
TH BMD (g/cm)	<b>0.616<math>\pm</math>0.091</b>	<b>0.716<math>\pm</math>0.097</b>	<b>0.736<math>\pm</math>0.148</b>	<b>0.830<math>\pm</math>0.115</b>
p	<10 <sup>-4</sup> *	<10 <sup>-4</sup> *	<10 <sup>-4</sup>	
Hmean	<b>0.583<math>\pm</math>0.032</b>	<b>0.607<math>\pm</math>0.037</b>	<b>0.599<math>\pm</math>0.035</b>	<b>0.625<math>\pm</math>0.028</b>
p	<10 <sup>-4</sup> *	0.028*	<10 <sup>-4</sup>	
Run-length	<b>2.222<math>\pm</math>0.077</b>	<b>2.249<math>\pm</math>0.074</b>	<b>2.245<math>\pm</math>0.069</b>	<b>2.286<math>\pm</math>0.063</b>
p	<10 <sup>-4</sup> *	0.011*	<10 <sup>-4</sup>	
Co-occurrence	<b>2.720<math>\pm</math>0.099</b>	<b>2.766<math>\pm</math>0.082</b>	<b>2.755<math>\pm</math>0.094</b>	<b>2.817<math>\pm</math>0.079</b>
p	<10 <sup>-4</sup> *	0.02*	10 <sup>-4</sup>	

\*: p values of the comparison between fracture cases and control cases using ANOVA adjusted for age

validated a fractal analysis based on the fractional Brownian motion [5]. In this latter study the fractal organization of our radiographic images was checked [5]. Clearly, whatever the fractal method used to analyse the bone texture, the main issues are to consider the adequation of the model to the images analyzed, the reproducibility, the discriminant capacity, the sensitivity to changes (treatments, diseases) and the capacity to improve the evaluation of osteoporotic fracture risk over that obtainable with known risk factors (age, body mass index, BMD, etc.). In this regard, we have found that our texture analysis has a good reproducibility [13], was sensitive to changes induced by osteoporosis treatments [15, 18], and differentiates postmenopausal women with and without fractures [11, 12].

The issue of whether bone texture analysis has the potential to assess some bone quality aspects complementary to and independent from bone density measurements is of great importance for the field of osteoporosis. Our study is consistent with previous studies showing the discriminant capacity of texture analysis in groups of control and osteoporotic subjects [11, 12]. Even though BMD is considered as one of the main contributors to bone strength other determinants of the so-called bone quality may also play a role: rate of bone turnover [19], degree of mineralization [20], size and quality of the crystal [21], distribution and quality of collagen cross links [22], microarchitecture [23], macroarchitecture [23]. Microarchitecture is one of the most relevant contributors of bone strength [24] and is part of the definition of osteoporosis.

Whether bone texture analysis (2D) reflects the trabecular bone microarchitecture (3D) is an important issue. Indeed for a long time, it has been proposed to extract microarchitectural information from bone pattern (texture) seen on plain radiographs [25, 26]. However the relationship between 2D texture parameters and 3D microarchitectural data has been discussed [9, 27]. We have demonstrated

that the Hmean parameter was related to the porosity and connectivity of micro MRI bone images [9]. In addition, Jennane et al. [28] have recently conducted a study which permitted to establish a formal link between the self similarity of a 3D fractal model and the self similarity of its 2D projection. This theoretical result was then applied to trabecular bone specimen digitized using a high resolution  $\mu$ CT and it was shown that a simple projection provided 3D information about the bone structure [28]. At least three other groups have highlighted the relevance of 2D analysis and the correlation between texture analysis of plain radiographs and the 3D bone microarchitecture [8, 10, 29]. Each of these works has concluded on the potential clinical interest of the bone texture analysis.

In this paper we confirmed the relative independence of texture parameters assessed at the calcaneus site from BMD values at the total hip, femoral neck and lumbar spine. These results are in line with previous analyses [13, 14]. We have previously studied the relationship between BMD and texture parameters in an accurately site-matched analysis at the calcaneus [13]. In this latter study we have found in this in vivo study significant but weak correlations between co-occurrence or run-length parameters and femoral neck BMD, respectively,  $r=-0.29$ ,  $p=0.03$  and  $r=-0.31$ ,  $p=0.03$ . Furthermore in another large study, including 427 women to assess the effects of age on bone texture parameters, we have also found a slight but significant correlation between Hmean and femoral neck BMD  $r=0.13$ ,  $p=0.008$  [15]. These results might be different in an in vitro study. Indeed, we can assume that some microarchitectural alterations evolving in the same way as BMD may be captured by density measurements.

Direct trabecular microstructure assessment is possible in vivo by high resolution peripheral quantitative computed tomography HR pQCT [30] or by magnetic resonance imaging [31]. However, trabecular microarchitecture as-

assessment is not feasible on standard MRI device. The use of HR pQCT would allow to characterize alterations of cortical and trabecular structure [30]. In their paper Sornay-Rendu et al. [32] using this device have found similar alterations at the distal radius and tibia than those evidenced by histomorphometric studies [33, 34] at the iliac crest in osteoporosis cases with fracture. However in the logistic model used to associate microarchitecture values and fracture status, after the adjustment for ultradistal radius areal BMD, there was only a trend for an increased risk of fracture [32]. Furthermore HR pQCT provides several parameters, while the clinician needs a simple and unique evaluation.

There are some limitations in our study. The cross-sectional design of our study did not allow us to conclude about the ability of our texture analysis to predict fracture risk in terms of relative risk, but the OR evaluation is considered to offer a good approach of this aspect. Texture parameters have been found correlated with some known descriptors of bone structure [6, 8]; however, they are only a reflect of the 3D structure. This texture analysis does not explore the cortical bone, even though cortical parameters are involved in osteoporotic fractures. The strength of our study is its multicenter design, which permitted to include a clinically detailed sample of post-menopausal women with or without fracture, who do not take any treatment except calcium and vitamin D.

In conclusion, this study suggests that some micro-architectural alterations reflected by bone texture parameters (non-invasively assessed by our high-resolution digital X-ray device) may improve estimation of the risk of fracture other than that obtainable by BMD. We have now to confirm these findings in prospective studies.

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**Conflicts of interest** None.

## References

- Marshall D, Johnell O, Wedel H (1996) Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 312:1254–1259
- Cummings SR, Nevitt MC, Browner WS et al (1995) Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 332:767–773
- Schuit SC, van der Klift M, Weel AE et al (2004) Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone* 34:195–202
- Wainwright SA, Marshall LM, Ensrud KE et al (2005) Study of Osteoporotic Fractures Research Group. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 90:2787–2793
- Benhamou CL, Lespessailles E, Jacquet G et al (1994) Fractal organization of trabecular bone images on calcaneus radiographs. *J Bone Miner Res* 9:1909–1918
- Lespessailles E, Roux JP, Benhamou CL et al (1998) Fractal analysis of bone texture on os calcis radiographs compared with trabecular microarchitecture analyzed by histomorphometry. *Calcif Tissue Int* 63:121–125
- Lespessailles E, Jullien A, Eynard E et al (1998) Biomechanical properties of human os calcanei: relationships with bone density and fractal evaluation of bone microarchitecture. *J Biomech* 31:817–824
- Guggenbuhl P, Bodic F, Hamel L et al (2006) Texture analysis of X-ray radiographs of iliac bone is correlated with bone micro-CT. *Osteoporos Int* 17:447–454
- Pothuaud L, Benhamou CL, Porion P et al (2000) Fractal dimension of trabecular bone projection texture is related to three-dimensional microarchitecture. *J Bone Miner Res* 15:691–699
- Luo G, Kinney JH, Kaufman JJ et al (1999) Relationship between plain radiographic patterns and three-dimensional trabecular architecture in the human calcaneus. *Osteoporos Int* 9:339–345
- Pothuaud L, Lespessailles E, Harba R et al (1998) Fractal analysis of trabecular bone texture on radiographs: discriminant value in postmenopausal osteoporosis. *Osteoporos Int* 8:618–625
- Benhamou CL, Poupon S, Lespessailles E et al (2001) Fractal analysis of radiographic trabecular bone texture and bone mineral density: two complementary parameters related to osteoporotic fractures. *J Bone Miner Res* 16:697–704
- Lespessailles E, Gadois C, Lemineur G et al (2007) Bone texture analysis on direct digital radiographic images: precision study and relationship with Bone Mineral Density at the os calcis. *Calcif Tissue Int* 80:97–102
- Chappard D, Pascaretti-Grizon F, Gallois Y et al (2006) Medullar fat influences texture analysis of trabecular microarchitecture on X-ray radiographs. *Eur J Radiol* 58:404–410
- Lespessailles E, Poupon S, Niamane R et al (2002) Fractal analysis of trabecular bone texture on calcaneus radiographs: effects of age, time since menopause and hormonal replacement therapy on microarchitectural changes. *Osteoporosis Int* 13:366–372
- Haralick R (1986) Statistical image texture analysis. In: *Handbook of pattern recognition and image processing*. Academic Press, San Diego, pp 247–279
- Vokes TJ, Giger ML, Chinander MR et al (2006) Radiographic texture analysis of densitometer-generated calcaneus images differentiates postmenopausal women with and without fractures. *Osteoporos Int* 17:1472–1482
- Benhamou CL, Chappard C, Gadois C et al (2004) Characterization of trabecular micro-architecture improvement under teriparatide by a fractal analysis of texture on calcaneus radiographs. *J Bone Miner Res* 19(Suppl 1):S126–SA113
- Heaney R (2003) Is the paradigm shifting? *Bone* 33:457–465
- Meunier PJ, Boivin G (1997) Bone mineral density reflects bone mass but also the degree of mineralization of bone: therapeutic implications. *Bone* 21:373–377
- Paschalis EP, Betts F, Dicarolo E et al (1997) FTIR micro-spectroscopic analysis of normal human cortical and trabecular bone. *Calcif Tissue Int* 61:480–486
- Viguet-Carrin S, Garnero P, Delmas PD (2006) The role of collagen in bone strength. *Osteoporosis Int* 17:319–336
- Seeman E, Delmas PD (2006) Bone quality - the material and structural basis of bone strength and fragility. *N Engl J Med* 354:2250–2261
- Briggs A, Greig A, Wark (2007) The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. *Osteoporos Int* 18:575–584
- Singh M, Nagrath AR, Maini PS (1970) Changes in trabecular pattern of the upper end of the femur as an index of osteoporosis. *J Bone Joint Surg* 52A:457–467
- Jhamaria NL, Lai KB, Udawat M et al (1983) The trabecular pattern of the calcaneus as an index of osteoporosis. *J Bone Joint Surg* 65:195–198
- Jennane R, Ohley WJ, Majumdar S et al (2001) Fractal analysis of bone X-ray tomographic microscopy projections. *IEEE Trans Med Imag* 20:443–449

28. Jennane R, Harba H, Lemineur et al (2007) Estimation of the 3D self-similarity parameter of trabecular bone from its 2D projection. *Med Image Anal* 11:91–98
29. Apostol L, Boudousq V, Basset O et al (2006) Relevance of 2D radiographic texture analysis for the assessment of 3D bone micro-architecture. *Med Phys* 35:46–3556
30. Boutroy S, Bouxsein M, Munoz F et al (2005) In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 90:6508–6515
31. Newitt DC, Majumdar S, van Rietbergen B et al (2002) In vivo assessment of architecture and micro-finite element analysis derived indices of mechanical properties of trabecular bone in the radius. *Osteoporos Int* 13:6–17
32. Sornay-Rendu E, Boutroy S, Munoz F et al (2007) Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY Study. *J Bone Miner Res* 22:425–433
33. Kimmel DB, Recker RR, Gallagher JC et al (1990) A comparison of iliac bone histomorphometric data in post-menopausal osteoporotic and normal subjects. *Bone Miner Res* 11:217–235
34. Foldes J, Parfitt AM, Shih MS et al (1991) Structural and geometric changes in iliac bone: relationship to normal aging and osteoporosis. *J Bone Miner Res* 6:759–766