

## RESEARCH

# Development of a prediction tool for low bone mass based on clinical data and periapical radiography

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**Objectives:** This study aimed to develop and test a tool for low bone mass pre-screening by combining periapical radiographs with clinical risk factors.

**Methods:** The study sample consisted of 60 post-menopausal women over 40 years of age who were referred for dental radiographs. These patients also had their bone mineral density measured at the lumbar spine and proximal femur using dual-energy X-ray absorptiometry. Radiographic density measurements and 14 morphological features were obtained from each dental radiograph using digital image processing software. The clinical variables considered were age and bone mass index. Classification and regression tree analysis (CART) was used to test the predictive power of clinical and radiographic risk factors for classifying individuals.

**Results:** CART indicated that the most important variables for classifying patients were age, number of terminal points/periphery, periphery/trabecular area, radiographic density and bone mass index.

**Conclusion:** A combination of clinical and radiographic factors can be used to identify individuals with low bone mineral density, with higher accuracy than any one of these factors taken individually.

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**Keywords:** bone density; osteoporosis; dental radiography

## Introduction

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of the bone tissue leading to enhanced bone fragility and increased risk of fracture.<sup>1</sup> Due to an aging population, osteoporosis can be considered as one of the major public health diseases, affecting 30% of post-menopausal women.<sup>2</sup> Measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry has been considered the main method of diagnosing osteoporosis. The World Health Organization (WHO) characterizes an osteoporotic individual as exhibiting a BMD greater than 2.5 standard deviations (SD) below the young adult mean value BMD.<sup>3</sup> However, this technique involves specific equipment that is only available at specialist diagnostic imaging centres.

Furthermore, the operational costs involved in these examinations are quite high, limiting their usefulness for annual screening of all post-menopausal women in a population.<sup>4</sup> Consequently, women are usually selected for bone densitometry based on clinical risk factors such as age, fracture history since menopause, low bone mass index and long-term corticosteroid use.<sup>5–12</sup>

It is well known that osteoporosis results in the alteration of the mandibular structures, especially the mandibular cortex.<sup>13–23</sup> Recent studies have linked osteoporosis to alterations of the trabecular bone, visible in dental radiographs.<sup>24–28</sup> Periapical radiographs are relatively inexpensive exams that are often available in dental offices. Since the trabecular bone can be easily visualized in periapical radiographs it is likely that, in common with other parts of the skeleton, this may contain important information about the bone's condition on a microstructural level. As a consequence, dentists would be able to identify patients

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at risk of developing osteoporosis by processing their periapical radiographs.

The aim of this study was to develop and test a tool for low bone mass pre-screening with high indices of sensitivity and specificity, combining periapical radiographs with clinical risk factors.

## Materials and methods

### *Patient sample*

The sample consisted of 60 post-menopausal women over 40 years of age who were referred to the Dental Radiology Service at the Universidade Federal do Rio Grande do Sul (UFRGS) School of Dentistry for periapical radiographs of mandibular premolar and/or molar regions during a 12 month period. Patients also had to have had their BMD evaluated at the lumbar spine and proximal femur within a 6 month period. Informed consent was obtained from all patients in the study, which was approved by the UFRGS Ethics Committee.

### *Bone mineral density*

All patients had BMD of the femur and lumbar spine measured by dual-energy X-ray absorptiometry (DPX-alpha, Lunar Co., Madison, WI). Patients were classified into one of two groups according to the results of BMD. The normal group contained women who were classified as normal according to the WHO classification (T-score greater than  $-1.0$ ). The low bone mass group contained women who were classified as osteopenic (T-score between  $-1.0$  and  $-2.5$ ) or osteoporotic (T-score less than  $-2.5$ ).

### *Radiographic jaw density*

An 8-step aluminium step wedge (1.0 mm to 8.0 mm thickness) was fixed under the biting surface of an intraoral positioning device using acrylic resin. Periapical radiographs were taken using Ektaspeed Plus film (Kodak, São Paulo, Brazil) with Pro 70 Intra<sup>®</sup> X-ray equipment (Prodental Dentistry Equipment Ltda, São Paulo, Brazil) using 70 kVp, 8 mA and variable exposure time. The radiographs were processed by a Dent X 9000<sup>®</sup> automatic film processor (Dent X, Elmsford, NJ). All resulting radiograph images were digitized at 600 dpi spatial resolution and 8-bit depth contrast resolution using an Epson Perfection 2450<sup>®</sup> flatbed scanner (Epson, Long Beach, CA) and saved in Bitmap file format (BMP). The polygonal Lasso Tool available in Photoshop CS 8.0 software (Adobe Systems Inc., San Jose, CA) was used to define the regions of interest (ROI). Interdental ROIs included: the interdental bone between premolars and molars or between the second premolar and first molar, according to the largest visible area; and from the alveolar crest to the level of apices, excluding the crestal bone and lamina dura. All measurements were made by a dental

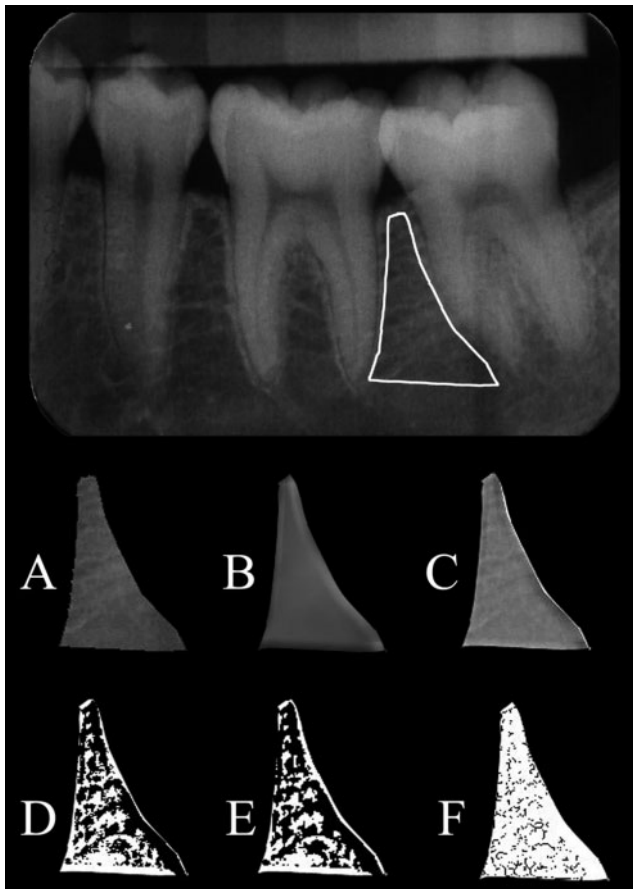
radiology specialist under standardized observing conditions. The mean grey level, SD and median value were measured using the histogram tool available in Photoshop CS 8.0, for each step of the step wedge and ROI. The resulting values were calculated as an equivalent to aluminium step wedge thickness by a simple linear interpolation rule.

### *Trabecular morphologic analysis*

An algorithm based on White and Rudolph's<sup>24</sup> description was developed to obtain 14 morphologic parameters from each digitized periapical radiograph. The algorithm runs in MatLab 7.1 software (MatWorks, Natick MA) and performs a sequential procedure of segmentation and morphological operators on the ROI of each image. Initially, the operator specified the same ROI that had been used for the radiographic jaw density measurement. A low-pass image was obtained from the original image by means of convolution of the ROI with a Gaussian Filter with a sigma of 35 and kernel  $33 \times 33$  pixels. This was intended to remove the artifacts typically found in low frequency spatial components. After this the filtered image was subtracted from the original, and the high frequency components were preserved. Next, the image was made binary with a threshold operation with a brightness value of 128. The resulting image was eroded and dilated once to remove noise. The image was then inverted to make the trabeculae apparent and then skeletonized, that is, eroded until only the central line remains (Figure 1). Finally, the skeletonized binary image was used to determine the morphologic features that characterized the trabeculae as follows:

- M1 Trabecular area / total area
- M2 Periphery / total area
- M3 Periphery / trabecular area
- M4 Length / trabecular area
- M5 Length / total area
- M6 Terminal points / cm<sup>2</sup>
- M7 Terminal points / length
- M8 Terminal points / periphery
- M9 Terminal points / trabecular area
- M10 Branch points / cm<sup>2</sup>
- M11 Branch points / length
- M12 Branch points / periphery
- M13 Branch points / trabecular area
- M14 Branch points / terminal points.

The trabecular area is represented by the total number of black pixels in the binary image divided by the total number of pixels in the ROI. The periphery is represented by the total number of pixels on the outer border of the trabeculae in the binary images, presented as a proportion of the total area of the trabeculae or of the total ROI. The skeletonized image was used to compute the total length of the skeletonized trabeculae (total number of black pixels), the number of terminal points (free ends, that is, black pixels with only one adjacent black pixel), and the number of branch points



**Figure 1** Sequence image procedure. (A) Region of interest; (B) Low-pass filter application; (C) Subtracted image (A–B); (D) Binary image made from C; (E) Noise reduction; (F) Skeletonized image.

(crossing points, that is, black pixels with three or more adjacent black pixels). These parameters are expressed as a proportion of trabecular length, area and perimeter.

#### Clinical data

The patients answered a questionnaire on the clinical risk factors for osteoporosis, including, age, height, weight, race, hormonal condition, family history of osteoporosis, calcium intake, exercise, smoking habits, caffeine intake, medicines and chronic diseases. Only post-menopausal women without systemic diseases were included in this study. The clinical risk factors considered in this study were age, weight, height and bone mass index.

#### Statistical analysis

Mean, median, SD, minimum and maximum values were determined for all variables in each group using SPSS 13.0 (SPSS Inc., Chicago, IL). The non-parametric Mann–Whitney test ( $\alpha = 1\%$ ) was used to compare clinical and radiographic factors between normal and low bone mass groups. Classification and regression tree analysis (CART) was used for clinical and radiographic factors to classify patients as belong-

ing to normal or low bone mass categories. To perform CART homonymous software was used (CART 6.0, Salford Systems, San Diego, CA). The use of binary decision trees can be described as a non-parametric approach for recognition of patterns.<sup>29,30</sup> The main components of CART are nodes and decision rules. At the start, all individuals are considered together at the “root” of a prediction tree. The data are then split along the variable that results in the largest difference between the two successive “nodes” (in terms of percentage of low bone mass or normal individuals). In each daughter node, variables are again examined to find the predictor that results in the best split between low bone mass and normal individuals. Splitting continues until stopping criteria are reached or until further splitting does not improve the classification.<sup>25</sup> Through the prediction tool, sensibility, specificity and accuracy values were obtained. Weighted kappa was used to assess agreement between the actual and predicted BMD categories. The accuracy of each separate variable was determined by its respective receiver operating characteristic curve.

#### Study error

The repeatability of the method was obtained by repeating all assessments in 20% of the sample. Student’s *t*-test for paired samples and Pearson’s correlation coefficient were used to test it. There was no significant difference for any variable ( $\alpha = 1\%$ ) and all the correlation coefficients were higher than 0.8.

#### Results

Of the 60 patients, 22 (mean age 49.9 years, range 40.0–49.9) were classified as normal according to BMD (T-score greater than  $-1.0$ ), and 38 (mean age 54.2, range 40.0–54.20) were classified as being in the low bone mass group (T-score  $-1.0$  to  $-2.5$  for osteopenia; T-score less than  $-2.5$  for osteoporosis). There was no significant difference between normal (Group I) and low bone mass groups (Group II) for any of the radiographic variables. The only clinical variable that was statistically significantly different was age (Table 1).

The CART analysis of clinical and radiographic features indicated that the most important factors for classifying subjects as having normal or low bone mass were age ( $\pm 42.5$  years) and number of terminal points as a function of periphery ( $\pm 0.09$ ) (Figure 2). This algorithm correctly identified all 22 patients who were considered normal by BMD (specificity = 100%). 31 of the 38 patients with low bone mass were correctly identified (sensitivity = 81%). The total accuracy was 88.33%. The weighted kappa index, a measure of the agreement between the predicted and actual bone category, was 0.76 (CI = 0.603, 0.927). When assessed separately, the most important variables showed low accuracy according to the area under curve Az (Table 2).

**Table 1** Comparison between normal and low mass groups (Mann-Whitney test)

	Median Group I (normal <i>n</i> = 22)	Median Group II (low bone mass, <i>n</i> = 38)	<i>P</i>
Age	50.500	54.500	0.047
Height	1.650	1.620	0.199
Weight	66.000	62.000	0.096
Bone mass index	24.375	23.520	0.195
RD	3.820	3.800	0.158
M1	0.570	0.589	0.927
M2	0.062	0.056	0.581
M3	0.109	0.097	0.634
M4	0.084	0.077	0.701
M5	0.050	0.046	0.640
M6	2387682	1827888	0.374
M7	0.082	0.072	0.241
M8	0.068	0.062	0.206
M9	0.007	0.005	0.399
M10	25051822	23836090	0.613
M11	0.918	0.928	0.241
M12	0.759	0.784	0.159
M13	0.077	0.072	0.730
M14	114309	128172	0.282

## Discussion

There is a consensus that BMD should be used for operational definition of the degree of osteoporosis. Dual X-ray absorptiometry is the standard technique for determining BMD. Because of the relative high costs and limited availability of dual-energy X-ray absorptiometry equipment it is worth looking for alternative diagnostic techniques.<sup>31</sup> Periapical radiographs are relatively inexpensive and are frequently taken in dental offices as an aid to diagnosis.

The present study found that the combination of age and features of the trabecular morphology of interdental bone was useful in identifying post-menopausal women with low bone mass. This finding is consistent with Lee and White.<sup>25</sup> In both studies age was the most important clinical predictor for loss of bone mass. Age is considered to be one of the most important clinical risk factors for osteoporosis.<sup>5,8</sup>

In this study the lamina dura and periodontal ligament were avoided during the selection of the ROI, although a recent study stated that there is no difference in the results when they are included.<sup>28</sup>

Several authors have used self-administered questionnaires for assessment of osteoporosis based entirely on clinical risk factors.<sup>32-35</sup> Geusens *et al*<sup>36</sup> examined the ability of four published osteoporosis risk indices to identify women with low bone mass. In another study, Horner *et al*<sup>37</sup> used the simple calculated osteoporosis risk estimation (SCORE) clinical index combined with the mental index (MI) index. The authors found that the inclusion of clinical information added value to measurements of the thickness of the mandible for identifying individuals with low bone mass.

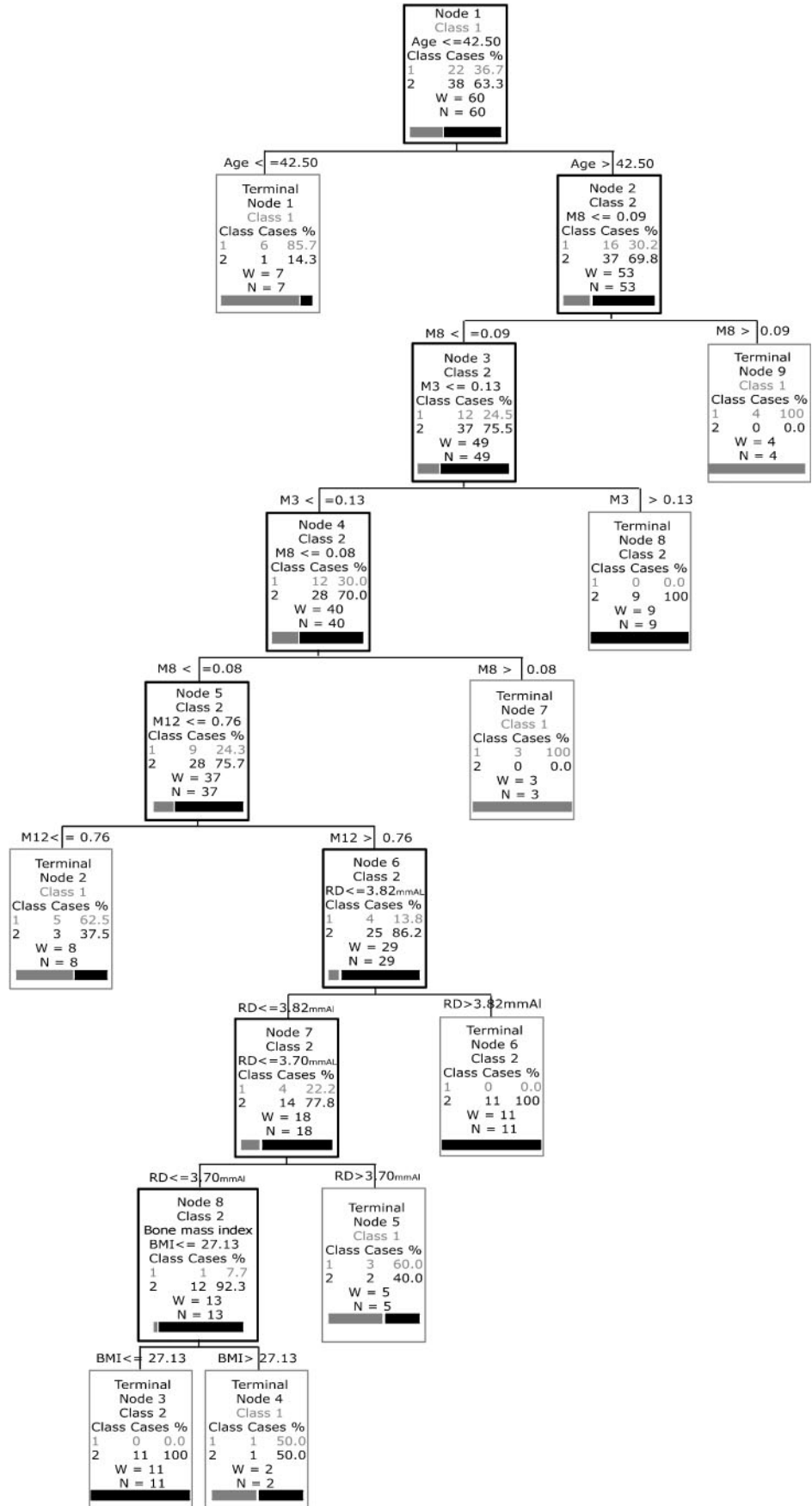
In addition to age, trabecular morphology analysis was an important factor for identifying women with low BMD. Osteoporosis results in low bone mass and microarchitectural deterioration that is characterized by thinning of residual trabeculae and loss of trabecular connectivity. Morphological findings of the femur and spine trabecular bone of patients with osteoporosis and of normal subjects have already been reported in previous studies.<sup>38-45</sup> The present study found subtle alterations in the mandibular trabecular pattern that were characterized by a reduction in trabeculae length, branch points and terminal points; however, this was not found to be statistically significant. This finding is not consistent with the study of White and Rudolph,<sup>24</sup> perhaps because of the different criteria used to select the sample. In that study<sup>24</sup> the test group consisted of women with a positive diagnosis of osteoporosis (mean age 63 years), while the control group consisted of younger women (mean age 39 years), whereas in the present study both normal and low bone mass groups consisted of postmenopausal women with similar mean ages, although in some cases the women's age corresponds to the pre-menopausal and peri-menopausal periods.

Furthermore, in this study a great number of patients in the low bone mass group had a diagnosis of osteopenia. Groups with greater differentiation, in terms of bone status, would have been necessary for this study to find statistical differences in the trabecular parameters. Of all the trabecular features assessed in this study, the number of terminal points/periphery, followed by periphery/trabecular area and branch points/periphery were the morphological variables that best identified patients with normal or low bone mass. This finding is consistent with other studies.<sup>24,25</sup> It is probable that the number of terminal points better reflects the complexity of trabecular connectivity, since with bone loss there is a reduction in the number and thickness of the trabeculae. The fractal dimension analysis of the mandibular bone in digital panoramic radiographs was not able to demonstrate differences among patients with normal or low bone mass.<sup>46</sup>

Mandibular bone density was one of the most important radiographic factors in the construction of the CART analysis. It is possible that a reduction in bone mass, represented in this study by reduction in trabecular complexity, causes a decrease in bone density. Therefore, radiographic jaw density and trabecular morphologic features are important variables for the prediction of low bone mass.

When clinical and radiographic factors were analysed separately, they were not capable of classifying patients as having normal or low bone mass. These results are in agreement with the low Az when variables were taken in isolation; however, when all the variables were taken together overall accuracy was satisfactory. This is consistent with the results of White<sup>20</sup> and more recently with Nackaerts *et al*,<sup>47</sup> who suggested the inclusion of





**Figure 2** Classification and regression tree (CART) results for clinical and dental radiographic features as predictors of low bone mass. The top cell contains all study subjects. At each split, the variable that produces the most favourable division of the data is indicated, along with the levels of the variable at which the best split occurs. Age is the most effective clinical variable for separating normal and low bone mass subjects. Terminal points/periphery (M8) is the most useful morphologic variable for separating normal and low bone mass subjects.

**Table 2**  $A_z$  value obtained by ROC curve for each variable

	Cut-off value	$A_z$	$P$	Confidence interval 95%
M12	0.76	0.630	0.100	0.478–0.783
Age	42.5	0.623	0.114	0.468–0.768
Bone mass index	27.13	0.603	0.187	0.449–0.756
RD	3.70	0.600	0.198	0.453–0.748
M8	0.08	0.597	0.214	0.442–0.752
M3	0.13	0.500	1.000	0.347–0.653

additional variables as clinical and morphologic radiographic factors in the screening for osteoporosis.

There are some limitations inherent to the design of this study. First, the sample size is modest, particularly in terms of the number of patients with osteoporosis.

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