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ORIGINAL ARTICLE

New technology REMS for bone evaluation compared to DXA in adult women for the osteoporosis diagnosis: a real-life experience

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Abstract

Summary Osteoporosis is a prevalent skeletal disorder in postmenopausal women. REMS represents a potential technology for osteoporosis diagnosis in clinical practice.

Objective To assess the accuracy of Radiofrequency Echographic Multi Spectrometry (REMS) technology in diagnosing osteoporosis in comparison with dual X-ray absorptiometry (DXA) on a population of Brazilian women.

Methods A population of women age ranged between 30 and 80 was recruited at DXA Service of São Paulo School-Hospital, Brazil. They underwent REMS and DXA scans at the axial sites. The REMS accuracy for the osteoporosis diagnosis was evaluated in comparison with DXA on both sites. The intra-operator and inter-operator coefficient of variation (CV) was also calculated.

Results A total of 343 patients were enrolled in the study. Erroneous scans due to poor quality acquisitions with both methods or to other technical reasons were excluded; 227 lumbar spine exams and 238 hip exams were acceptable for comparison analysis. The comparison between REMS and DXA outcomes showed that the average difference in BMD (expressed as bias±1.96 SD) was −0.026±0.179g/cm^2 for the spine and −0.027±0.156g/cm^2 for the femoral neck. When accepted 0.3 tolerance on T-score, there were no cases diagnosed as osteoporosis by DXA that were defined as normal by REMS. The REMS intra-operator CV was 0.51% for the lumbar spine and 1.08% for the femoral neck. The REMS inter-operator CV was 1.43% for the lumbar spine and 1.93% for the femoral neck.

Conclusion The REMS approach had high accuracy for the diagnosis of osteoporosis in comparison with DXA in adult women. According to our results, this new technology has shown to be a promising alternative for populations without access to DXA densitometry.

Keywords Osteoporosis diagnosis · Radiofrequency Echographic Multi Spectrometry (REMS) · Bone mineral density · Ultrasound · Dual X-ray absorptiometry (DXA)

Introduction

Osteoporosis is a systemic disease associated with bone fragility [1]. There is an increasing awareness regarding osteoporosis due to its association with subsequent fractures, with the consequent reduction in independence and elevated mortality [2], but also because it is a treatable disease. Postmenopausal women are high risk for osteoporosis, and approximately 50% of women will experience at least one bone fracture after the age of 50 [3, 4].

In many countries, the current approach is to screen women who are in their sixties for clinical risk factors and bone mass density (BMD), assessed by dual X-ray absorptiometry (DXA) [3]. BMD is one of the most consistent predictors of bone fracture risk [5].

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DXA is the standard method used to define osteoporosis, according to the criteria defined by the World Health Organization (WHO) in 1994 [5]. Since then, the scientific health community has accumulated a robust experience with this method, which provides good precision and reproducibility, and it is used worldwide.

However, DXA presents some disadvantages: use of X-ray, lack of portability, the need of highly specialized technical personnel, and a dedicated room, large enough to keep the operator more than 1 m from the X-ray source, thus reducing its accessibility to specifically equipped locations [6, 7]. Other limiting factors must be considered: the presence of artifacts such as osteophytes secondary to osteoarthritis, aortic calcification, and bone fractures that can lead to an overestimation of the bone mineral density value and the limited information regarding the bone microstructure, not to mention the improper quality control of the DXA scan that can be affected by pre- and post-processing image defects [8–11]. Thus, alternative technologies for bone evaluation have been sought after to complement or to be an alternative to DXA.

Radiofrequency Echographic Multi Spectrometry (REMS) is a non-ionizing and portable method for axial bone evaluation wherein the principles are based on the analysis of the spectra of unfiltered ultrasound waves. They are acquired during an echographic scan which uses B-mode images to identify target bone interfaces and related ROIs. Each single echographic line has a radiofrequency (RF) signal automatically extracted, and the software is able to identify cartilage, cortical, and trabecular bone layers in the RF signal. The trabecular portion is selected for analysis, so signals corresponding to artifacts located on the cortical bone should not interfere with the results [12].

Each acquired signal spectrum is compared to previous derived reference models for pathological and normal condition. The calculated percentage of analyzed spectra that were classified as "osteoporotic" is defined by the Osteoporosis Score, a numerical parameter. This result is converted into BMD_{US} values through linear equations as well as to derive T-score and Z-score values through quantitative comparisons with the National Health and Nutrition Examination Survey (NHANES) reference curves [12, 13]. This technology was validated in both single-center and multicenter studies for osteoporosis diagnosis [12–14] and for assessing fracture prediction [15].

Based on these considerations and to better understand the applicability of this method, we compared BMD measured by both REMS and DXA in Brazilian women who were recruited at São Paulo Hospital, in São Paulo, Brazil. The aim was to assess the REMS diagnostic accuracy compared to DXA, its sensitivity and specificity in diagnosing osteoporosis, the diagnostic concordance, and the short-term intra-operator and inter-operator precision of the same method. Secondary objectives were to assess possible ethnicity and comorbidities interferences on BMD_{US} estimation.

Material and methods

Study design

This was a cross-sectional observational study conducted to assess the REMS diagnostic accuracy compared to DXA, its sensitivity and specificity in diagnosing osteoporosis, diagnostic concordance, and short-term intra-operator and inter-operator precision of the same method. Secondary objectives were to assess possible ethnicity and comorbidities interferences on BMD_{US}.

The subjects were recruited from June to August 2019 at the DXA Unit of São Paulo School-Hospital, at the Federal University of Sao Paulo. Following anthropometric assessments (weight, height, and body mass index calculation (BMI)), all subjects underwent lumbar spine and hip analysis by DXA and REMS. Reports of each site were processed separately. Regarding age, women older than 40 were classified using T-score and those younger, using Z-score. All exams were anonymized before being used for the statistical analysis.

Electronic medical reports available were reviewed for menopausal status, diabetes mellitus, rheumatoid arthritis, human immunodeficiency virus (HIV), chronic obstructive pulmonary disease (COPD), and malabsorptive intestinal syndrome. Ethnicity was self-reported.

Study subjects

This study was approved by the Research Ethics Committee of the Federal University of São Paulo and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included.

The inclusion criteria were female sex, aged 30–80 years old, body mass index (BMI) < 40 kg/m^2, and a referral to have DXA exam performed in the São Paulo Hospital. The exclusion criteria were pregnancy self-declared, the impossibility of adequate patient positioning, and failure to sign the consent form. After image collecting, reasons for DXA scan exclusions were errors of positioning, acquisition, analysis and demographics, and moderate or severe scoliosis by Cobb's classification. In addition, REMS exams presenting wrong or suboptimal transducer focus or scan depth settings and incorrect performance adherence to the on-screen audible indications provided by the software (e.g., missing or delayed movement from a given vertebra to the next one) were also excluded.

DXA

All DXA measurements were performed by two technicians with more than 10 years of experience in a Hologic Discovery Wi device (model Hologic QDR 4500, Waltham, MA, EUA).

The reported DXA least significant change (LSC) is 3.5% for the lumbar spine and 3.8% for the hip in DXA Service of São Paulo School-Hospital [16]. Positioning and image acquisition were performed according to the International Society for Clinical Densitometry (ISCD) protocol [17]. Bone mineral density (BMD) values (g/cm^2) and their respective T-score were obtained from the lumbar spine (L1–L4), femoral neck, and total hip for a diagnostic classification according to the WHO criteria [18] and the ISCD.

REMS

All REMS acquisitions were performed by two independent operators trained for this method with at least 4 months of previous clinical experience with REMS. The EchoStation model (Echolight Spa, Lecce, Italy) was equipped with an echographic convex probe, operating at the nominal frequency of 3.5 MHz, which detects unprocessed radiofrequency signals. Data processing implemented in the REMS technology have been described in previous papers [12, 13].

Lumbar scans were performed by placing the echographic transducer in a trans-umbilical line under the xiphoid process to visualize L1 lumbar vertebra and then moving it towards the umbilicus to analyze L4, according to software indication. Each vertebra of the lumbar scan lasted 20 s and was followed by an automatic processing time of about 1–2 min.

Hip scans were performed by positioning the echographic transducer on the head-neck axis of the femur to visualize the proximal femur profile. The scan lasted 40 s, and the processing time was about 60 s.

The transducer focus (21–100 mm) and scan depth (60–210 mm) were adjusted to each acquisition to fixate on the target bone interface (vertebral surface or femoral neck) in the ultrasound beam focal zone and at about halfway through the image depth (at a distance of at least 3 cm from image bottom). Those steps were taken for all the performed vertebral and hip acquisitions.

Only one capture attempt for each site was made. The focus and depth measurements were kept if a second image was done in the same patient for the purpose of measurement of intra- and inter-operator coefficients of variation.

Precision

The short-term intra-operator coefficient of variation (CV) was calculated for each anatomical site using data of the last 30 patients performed by the same operator [19]. The LSC for a 95% confidence level was also calculated as recommended by the ISCD.

The short-term inter-operator CV was assessed on the data acquired on the last 30 cases performed by the two operators. The LSC for a 95% confidence level was also calculated as recommended by the ISCD.

Data analysis

Statistical analyses were performed with the R Core Team program (2019). The Kolmogorov-Smirnov test was used to evaluate normality. Wilcoxon signed test was used since data obtained were not normally distributed. Continuous variables as age, height, weight, BMI, and BMD were presented as mean and standard deviation (SD). Intra- and inter-operator variations are not normally distributed, so comparisons were presented as median and interquartile intervals. For the same site, the degree of correlation between BMD of both methods was quantified through linear regression analysis and Pearson's correlation coefficient (r). Additionally, a Bland-Altman plot was used to evaluate test agreement. Sensitivity and specificity for osteoporotic and non-osteoporotic patients from 40 years old were performed to REMS (T-score). Additionally, the ability of REMS to discriminate osteoporosis was evaluated using ROC curve analysis. Diagnostic concordance between the two methods was assessed by calculating the percentage of patients being classified in the same diagnostic category (osteoporosis, osteopenia, or normal) by both DXA and REMS, applying the Cohen's kappa (k). Differences in BMD among ethnic groups were evaluated by multiple linear regression models adjusted for weight and age to control confounding variables and then, multiple Tukey test two by two, setting the 95% global confidence coefficient. The Student´s t-test was used to compare the clinical data and the BMD measured at each site by both methods. A p-value < 0.05 was considered statistically significant.

Results

There were 343 women aged between 30 and 80 recruited. Patient characteristics are shown in Table 1. A total of 41 DXA lumbar spine scans, 67 REMS lumbar spine scans, 30 hip DXA scans, and 63 hip REMS scans were excluded. Besides, 18 REMS exams had technical problems as the presence of colostomy (n=1), pain during the scan (n=2) and abdominal surgery scar (n=1) in lumbar spine scans, difficulties in identifying the bone structures (n=12), and scan device bugged in both sites scan (n=2), and 3 REMS missed exams, and 1 DXA missed exam. The cases with acceptable exams in both methods were used for comparisons, remaining 227 lumbar spine and 238 hip exams (Fig.1).

BMD values derived from the REMS method and from DXA were highly correlated in lumbar spine (r=0.75) and femoral neck (r=0.78), with statistical significance (p<0.001; Fig. 2). The corresponding Bland-Altman plot shows a mean difference ± 1.96 SD of −0.026±0.179 g/cm^2 for lumbar spine and −0.027±0.156 g/cm^2 for the femoral neck (Fig. 3).

Table 1 Patient characteristics

	Total (*n*=343)
Demographic data	
Age (years) (*n* = 343)	59.9 ± 10.2
Referred ethnicity (*n* = 322)	
Asian	27 (8.4%)
Caucasian	224 (69.6%)
African descendent	48 (14.9%)
Miscigenated	23 (7.1%)
Medical conditions	
Menopause (*n* = 251)	229 (91.2%)
Diabetes type 1 (*n* = 257)	4 (1.6%)
Diabetes type 2 (*n* = 256)	39 (15.2%)
Chronic obstructive pulmonary disease (*n* = 245)	8 (3.1%)
Rheumatoid arthritis (*n* = 255)	7 (2.7%)
Malabsorptive intestinal syndrome (*n* = 255)	13 (5.1%)
Human immunodeficiency vírus (*n* = 255)	10 (3.9%)
Anthropometric data	
Weight (kg) (*n* = 343)	65.0 ± 12.6
Height (cm) (*n* = 343)	153.4 ± 7.2
BMI (kg/m^2) (*n* = 343)	27.6 ± 4.6
Bone mineral density measurement	
DXA lumbar spine—T-score (*n* = 302)	−1.5 ± 1.3
REMS lumbar spine—T-score (*n* = 266)	−1.8 ± 1.0
DXA femoral neck—T-score (*n* = 312)	−1.1 ± 1.1
REMS femoral neck—T-score (*n* = 269)	−1.4 ± 1.0
DXA total hip—T-score (*n* = 312)	−1.1 ± 1.1
REMS total hip—T-score (*n* = 269)	−0.7 ± 1.0

mean ± SD; *n* (%)

For the diagnosis of osteoporosis in women older than 40 years, the REMS approach effectively discriminated the osteoporotic patients from the non-osteoporotic for both lumbar spine (sensitivity = 80%, specificity = 94%) and hip exams (sensitivity = 85%, specificity = 93%).

The ROC curve of REMS osteoporosis diagnosis (using DXA T-score as reference) resulted in the area under the curve (AUC) of 0.94 for the lumbar spine and 0.97 for the hip (Fig. 4).

Considering the diagnosis concordance of osteoporosis, osteopenia, and normal between both methods for patients above 40 years old, it was 67.1% for the lumbar spine (k=0.47) and 71.4% (k =0.53) for the hip.

As previous studies [14, 15], a 0.3 tolerance for T-score REMS borderlines was considered, so these cases were matched to DXA diagnoses. It was recalculated sensitivity and specificity for osteoporosis diagnosis and diagnostic concordance for the three categories described above, by kappa. For osteoporosis diagnosis, the sensitivity was 84%, and specificity was 94.6% for the lumbar spine; for the hip, sensitivity was 92.6%, and specificity was 93.5%. The values of diagnosis concordance and kappa rise for both sites: 69.4% (k= 0.51, p<0.001) for the lumbar spine and 74.9% (k= 0.58, p<0.001) for the hip.

The non-concordant diagnoses were concentrated on those DXA classified as normal and REMS classified as osteopenia. Considering the tolerance, they account for 57% (40 in 70 cases) on the lumbar spine exams and 31% (27 in 88 cases) on the hip exams.

The short-term intra-operator variability was 0.51% (95% confidence interval (CI): 0.38–0.64%), and LSC value was 1.41% for lumbar spine. For femoral neck, CV was 1.08% (95% CI: 0.80–1.35%), and LSC value was 2.99%. The short-term inter-operator analysis yielded a CV of 1.43% (95% CI: 1.25–1.62%) and LSC of 3.96% for lumbar spine. For femoral neck evaluation, CV was 1.93% (95% CI: 1.69–2.17%) and LSC was 5.35%. The BMD_{US} of lumbar spine and of femoral neck were highly correlated (r=0.92).

The body weight displayed a strong correlation with femoral neck BMD_{US} (r=0.91, p<0.001) more robustly than with BMI (r=0.76, p<0.001), even though BMI is used in the REMS database.

African descendent women had a higher adjusted BMD at all sites compared to Caucasian women. Besides, African descendent women displayed higher femoral neck BMD_{US} than Asian and miscigenated.

The BMDs in COPD and diabetes mellitus type 2 patients showed similar trends using both methods. The mean femoral neck BMD was higher for diabetics than non-diabetics. However, DXA obtained higher lumbar spine BMD for diabetics, while REMS showed no difference. On the other hand, COPD patients presented lower mean lumbar spine BMD using both methods but no differences in the femoral neck. Other assessed health conditions showed no significant differences.

Discussion

In this study, BMD from DXA and REMS analyses had high correlation and agreement. The Bland-Altman plots showed that the mean of the BMDs values of both methods were higher in the lumbar spine compared to the femoral neck exams. Besides, the difference between BMDs grows as the means increase. Outside the 95% confidence level, exams were more frequent among the highest means and mostly represented by cases in which BMD_{US} was lower than BMD. They consisted in 4.8% of lumbar spine exams and in 3.8% of femoral neck exams. Among these exams, those whose BMD difference resulted in a different diagnostic were only 1.8% of the lumbar spine and 1.7% of the femoral neck. These exams were individually assessed and it was not possible to establish any pattern, so more research must be carried

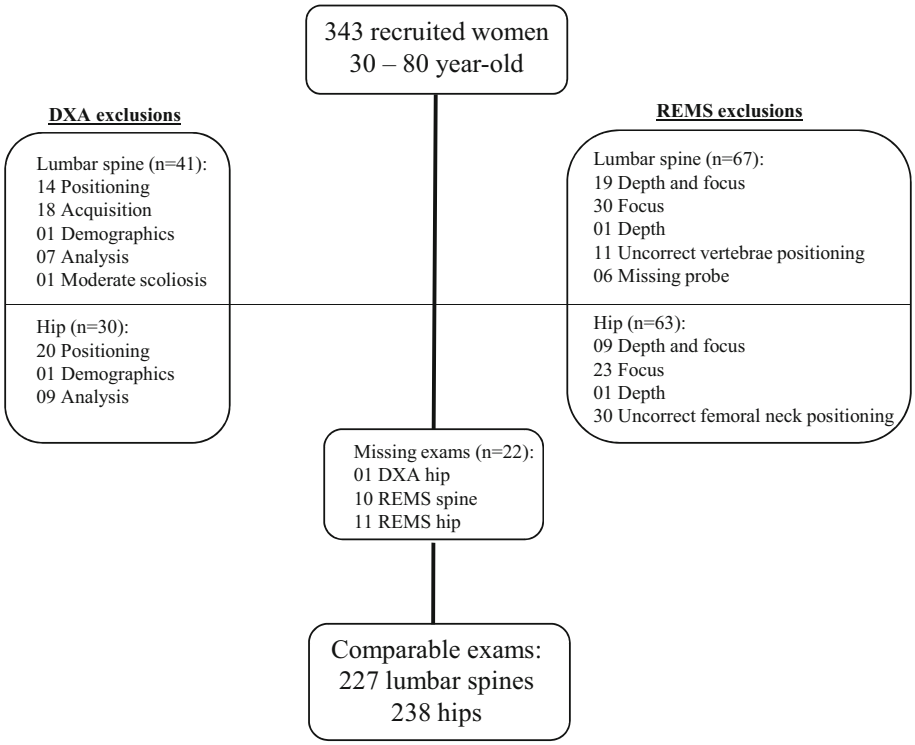

Fig. 1 Framework showing the comparison of the cases with acceptable exams in both methods

out to understand which factors influence exams that had a higher range from the mean BMD difference.

This method had high sensitivity and specificity in the osteoporosis diagnosis, and the area under the curve (AUC) was considered to represent good performance. No case of osteoporosis diagnosed by DXA was defined as normal by REMS. Considering a 0.3 tolerance in REMS borderline diagnoses, it was found that sensitivity increased up to 4% for the lumbar spine and up to 7.4% for the femoral neck and specificity was 0.6% for the lumbar spine and 1% for the femoral neck.

Degenerative processes on the lumbar spine and hip were not excluded from DXA exams. As the REMS analysis

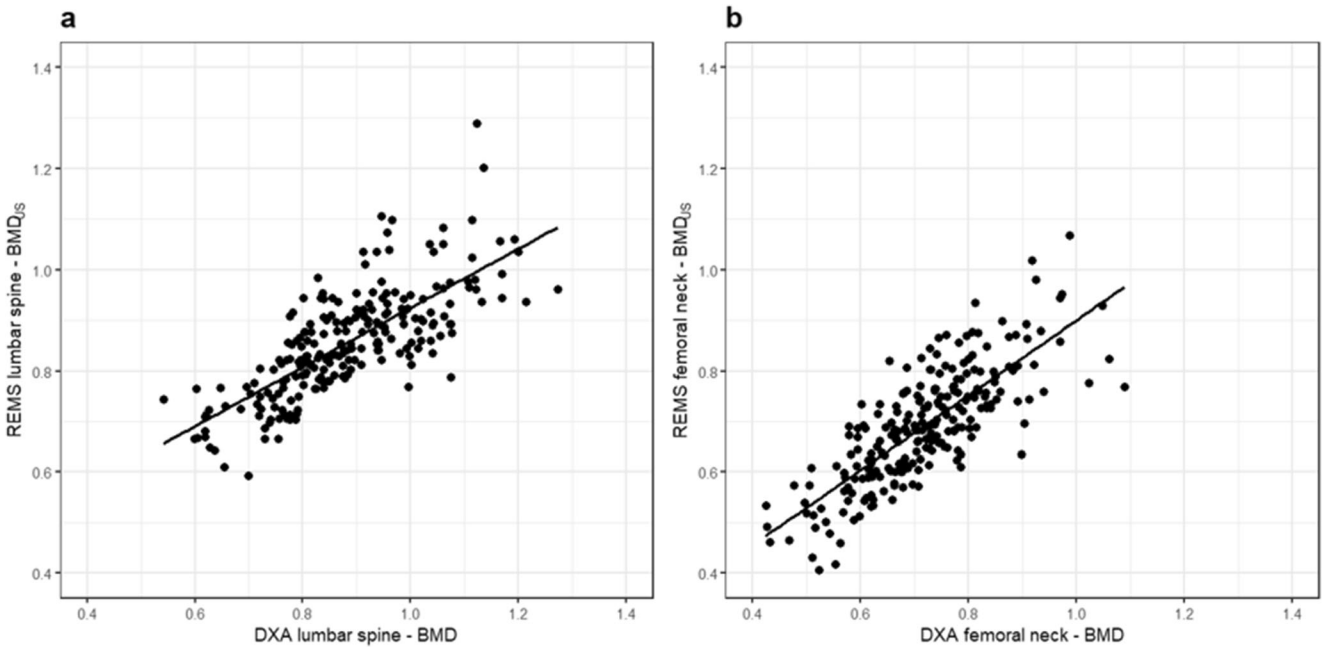

Fig. 2 Scatterplot of BMD and BMD_{US} : **a**. lumbar spine (r=0.75, p<0,001) and **b** femoral neck (r=0.78, p<0.001)

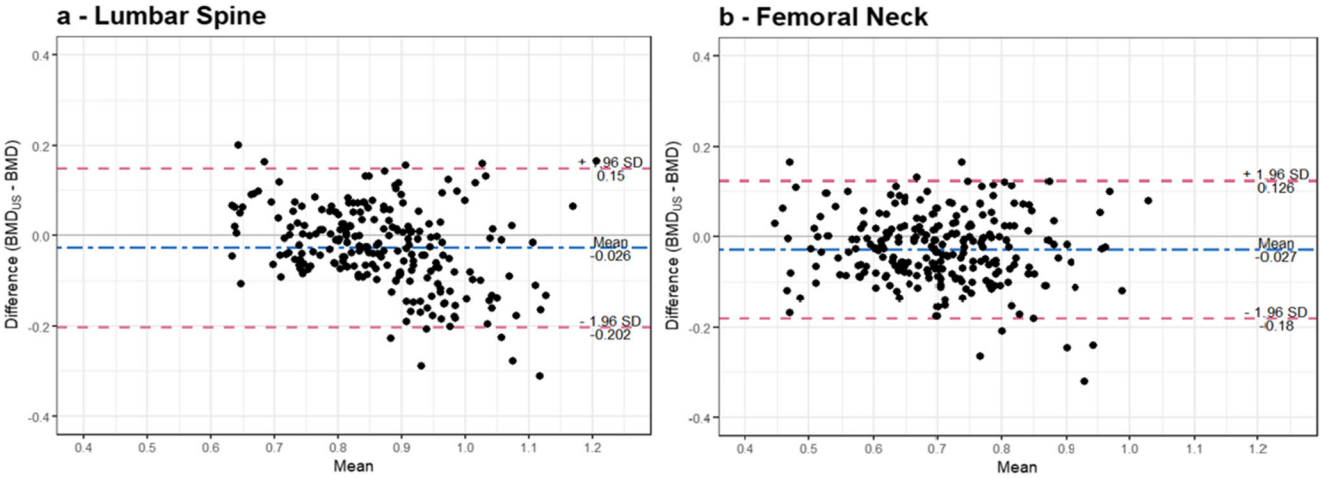

Fig. 3 Bland-Altman plot showing data of 227 lumbar spine and 238 femoral neck exams. The central lines indicate the mean BMD differences and the upper and lower lines represent the CI for 95% limits of agreement

process excludes osteophytosis and endplate sclerosis, it may have affected diagnosis concordance and contributed to the heterogeneity between normality and osteopenia diagnosis of both methods. Nevertheless, the diagnostic concordance between the two methods was lower compared to previous studies [14, 20]. Di Paola et al. [14] found results closer to ours in their supplementary dataset which contained all REMS reports, without any error exclusion, evaluating REMS in a "real life" context. In this data, the diagnosis concordance without a 0.3 tolerance reached 76.4% in lumbar spine and 81.9% in femoral neck.

Furthermore, it was essential to evaluate the short-term intra-operator and inter-operator to show the precision of the REMS method. The LSC values for both methods were good, especially compared to the literature report for DXA in the lumbar spine (2–4%) and the hip (3–6%) [21]. It shows the good precision of REMS and the narrow characteristic profile of the learning curves of the technicians and confirms the least dependence of the REMS results from the operator.

A high correlation was found between the BMD_{US} of the lumbar spine and the hip. In the common DXA practice, a discordance between femoral and lumbar spine T-score has been observed in about 40% of the cases [22, 23]. Possible causes may be due to REMS ability to exclude RF signals of cortical layer which may contain degenerative artifacts which overestimate the BMD. Furthermore, DXA has limitations related to bone size because it measures an areal density, what appears not interfere in BMD_{US}.

BMD_{US} is highly correlated to patient anthropometric data due to the comparative analysis of the patients' spectra with

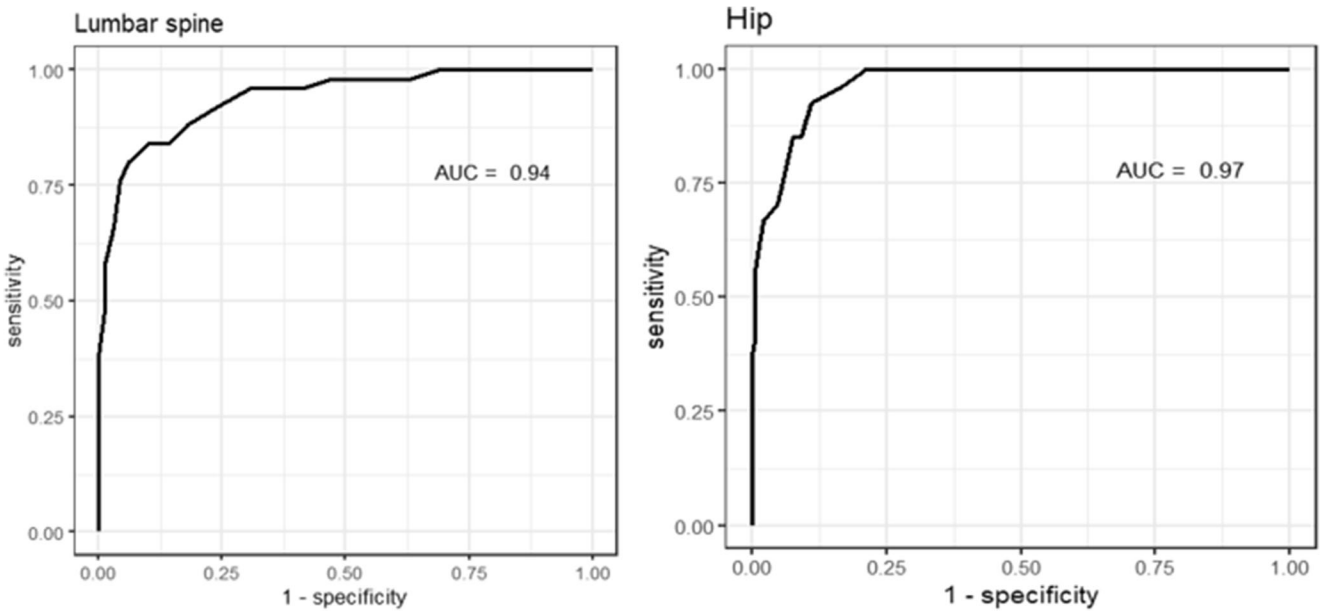

Fig. 4 The ROC curve of REMS osteoporosis diagnosis (using DXA T-score as reference)

the reference database, which considers the patient ethnicity, age, sex, and BMI. However, the correlation between weight and BMD_{US} is higher than the one with other parameters as age, BMI, and height, and such correlations are also higher than those obtained with DXA.

Differences in bone outcomes between African descendent and other ethnicities were detected by both methods. These data indicate the necessity of more studies underlying ethnicity.

Clinical diagnosis of COPD and type 2 diabetes had similar findings by both methods: lower lumbar spine BMD in COPD patients as described by M.G. Adas-Okuma et al. [24] and increased femoral neck bone mass in type 2 diabetes as described in the literature [25].

REMS experimental data have been recently gathered. After REMS multicentric validation, the strong results led the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) [26] to publish insights on REMS, which is an approach for osteoporosis diagnosis and fracture risk predictor. In another study, Adami et al. [15] demonstrated in a population of Caucasian women of 30–90 years old that REMS had higher sensitivity than DXA in classifying as osteoporotic those women who presented a fracture in a follow-up period up to 5 years. Also, a European multicentric study confirmed the high correlation between REMS and DXA analysis [20].

Fragility Score is a tool developed from REMS technology to determine bone quality and strength, independently of BMD. This parameter compares the patient-specific spectra to reference models for frail and non-frail bone spectra, thus giving a fracture risk estimation [27]. Greco et al. [28] found a good correlation between the Fragility Score and FRAX® for the fracture risk estimation (r=0.71, $p < 0.001$) in a female population. Researches involving clinical trials of osteoporosis treatment and REMS and Fragility Score are still expected.

Other researches continue to swell the ranks of publications on REMS. De Marco et al. [29] compared the bone apparent integrated backscatter (AIB) acquired by REMS with the trabecular bone volume (BV/TV) quantified by the micro-computed tomography on ex vivo femoral heads. Moderate statistically significant correlation was found (r= −0.69, p<0.00001) between the bone AIB and trabecular BV/TV. Khu and Sumardi [30] reported a significant correlation between BMI and the incidence of osteoporosis in the femoral neck (r = −0.69, p<0.01) and spine (r = −0.39, p<0.01). Bojincă et al. [31] found low lumbar spine and hip BMD_{US} in patients with rheumatoid arthritis compared to healthy post-menopause women controls.

This study is the first research on REMS technology in a Latin American population. We aimed for a real-life experience, so our study group was multiracial and had a broad age range, and osteodegenerative processes were maintained in DXA. One of the limitations of our study was the relative high number of REMS scans which were excluded due to wrong selection of depth/focus during echographic scanning, incorrect positioning of the bone target on the screen, and missing probe (19.5% for lumbar spines and 18.3% for hips acquisitions). Although the REMS's operators have been trained previously, it probably was not enough to complete their learning curve. Besides, according to our protocol, the REMS acquisitions were performed once and could not be repeated which usually does not happen in the daily clinic routine. Another limitation was DXA scan exclusions due to errors of acquisition, positioning and analysis, and demographic mistakes (11.6% for lumbar spines and 8.7% for hips acquisitions). There are remaining questions about REMS related to the identification of an eventual vertebral fracture at the site of the lumbar spine, since, unlike DXA, there is no image available, and further investigations are needed.

Conclusions

REMS represents a potential method for bone evaluation in clinical practice. In this cross-sectional observational study, REMS had high accuracy, sensitivity, and specificity for the diagnosis of osteoporosis compared to DXA and low coefficient of variation. Ongoing and future studies will assess REMS diagnostic performance in different diseases, ethnicities, and male populations and better understand its advantages and limitations.

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Declarations

The study design and its conduction were carried out by the research team without any interference from the manufacturer. The study was conducted following the ethical standards for clinical research in human beings and previously approved by the ethics and research committee of the Federal University of São Paulo (number 0252/2019).

Conflict of interest None.

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