Full Length Article

Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context

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\textbf{ABSTRACT}

\textbf{Background}: Radiofrequency Echographic Multi Spectrometry (REMS) is a non-ionizing technology for the densitometric assessment of osteoporosis. It has already been validated in Italian women with respect to the current clinical reference technology, Dual-energy X-ray Absorptiometry (DXA).

\textbf{Purpose}: Aim of the current study was to assess the diagnostic accuracy of REMS technology with respect to DXA in a wider European clinical context.

\textbf{Methods}: A total of 4307 female Caucasian patients aged between 30 and 90 years underwent DXA and REMS scans at femoral neck and/or lumbar spine (the site depending on the medical prescription). The acquired data underwent a rigorous quality check in order to exclude the erroneous DXA and REMS reports. The diagnostic agreement between the two technologies was assessed, also stratifying for patients’ age groups. The ability to recognize previously fractured patients was also investigated.

\textbf{Results}: Overall, 4245 lumbar spine scans and 4271 femoral neck scans were performed. The ability to discriminate patients with and without osteoporosis by femoral neck investigation resulted in sensitivity and specificity of 90.4% and 95.5%, respectively. For lumbar spine scans, a sensitivity of 90.9% and a specificity of 95.5% were obtained. The areas under the curve (AUCs) of the Receiver Operating Characteristic (ROC) curve evaluating the ability to discriminate groups of patients with previous osteoporotic fracture using DXA and REMS T-score values were 0.631 and 0.683 (p < 0.0001), respectively, for femoral neck scans, whereas 0.603 and 0.640 (p = 0.0002), respectively, for lumbar spine scans.

\textbf{Conclusion}: The diagnostic effectiveness of REMS technology at reference anatomical sites for the assessment of osteoporosis has been confirmed in a large series of female patients, spanning from younger and pre-menopausal to elderly women up to 90 years, in a multicenter European clinical context.

1. Introduction

Osteoporosis, a bone metabolic disease characterized by low bone mass and by alterations of macro- and micro-architecture of the skeletal tissue, is the main cause of fractures occurring over the age of 50 years as a result of non-traumatic injuries or low/medium energy traumas, commonly known as fragility fractures [1,2].

Over the last decades, the conception of this condition has evolved from being considered as an inevitable consequence of ageing to being recognised as a serious and treatable disease [3]. The prevention of...
incident fragility fractures and their potential sequelae of comorbidities, disabilities and the associated increased relative mortality is the primary goal of an improved osteoporosis management, in terms of early diagnosis and treatment monitoring [4]. It has been estimated that, in 2017, new fragility fractures in the largest five countries of the European Union (France, Germany, Italy, Spain and United Kingdom) plus Sweden were 2.7 million with an associated annual cost of €37.5 billion and a loss of 1.0 million quality-adjusted life years [5].

Primary care providers should routinely incorporate specific screening strategies for bone health assessment into wellness visits in post-menopausal women or earlier in case of specific conditions, such as diagnosis of a fracture, particularly of non-traumatic aetiology, or in presence of risk factors including premature menopause, chronic therapy with glucocorticoids, low body weight, family history of osteoporotic fractures, diseases that affect bone metabolism or excessive daily alcohol intake [6–9].

The diagnosis of osteoporosis basically relies on the measurement of bone mineral density (BMD) as the quantity of bone mass per unit of area or volume (areal BMD, measured as grams per square centimetre [g/cm²], or volumetric BMD, measured as grams per cubic centimetre [g/cm³], respectively). Among the variety of the currently available imaging techniques for the assessment of BMD, the clinical reference is Dual energy X-ray Absorptiometry (DXA), based on bone X-ray absorptiometry [9,10]; a detector measures the degree of attenuation of an incident X-ray that have passed through the patient’s tissues. As the properties of the tissue vary, the radiation will be attenuated differently, and the areal BMD (i.e. the ratio between bone mineral content and 2D projection of the scanned bone area), is calculated. The diagnosis of disease is obtained by comparing the individual results to a reference young healthy population, in terms of T-score [9,11].

Radiofrequency Echographic Multi-Spectrometry (REMS) is a relatively recent technology that performs the analysis of bone quantity and quality through a non-ionizing approach [12], being based on the analysis of ultrasound signal backscattering [13,14]. The BMD is calculated through advanced comparisons of the patient’s specific spectrum of the target bone against a proprietary database of reference ultrasound spectral models and the corresponding T-score and Z-score values are derived using a normative reference database, i.e. the National Health and Nutrition Examination Survey (NHANES) [12]. This approach has been validated through several national studies each time focused on specific age ranges [13–18].

The current study aimed to assess the diagnostic accuracy of the REMS technology with respect to DXA in a large European female population covering a very wide age range, with an additional focus on comparing the ability of the two technologies in the identification of the subjects with previous osteoporotic fractures.

2. Methods

2.1. Patients and measurements

This multicenter observational study involved the Hospital del Mar in Barcelona (Spain), the University Hospital of Florence in Florence (Italy), the Centre Hospitalier Universitaire (CHU) in Liège (Belgium), the Southampton General Hospital in Southampton (UK) and the Vita Fazzi Hospital in Lecce (Italy). The study protocol has been approved by the Ethics Review Boards of all the participating hospitals. All the enrolled patients voluntarily entered the study after giving written informed consent. The inclusion criteria were: female Caucasian patients; age between 30 and 90 years; medical prescription for spinal and/or femoral DXA; absence of significant deambulation impairments; signed informed consent. In order to compare the diagnostic effectiveness of the two methods in the real-life clinical routine, all other clinical situations were included. The patients underwent a spinal and/or femoral DXA investigation, according to their medical prescription, and an echographic REMS scan was performed at the same anatomical site. Before REMS and DXA acquisitions, the enrolled patients underwent a measurement of the anthropometric parameters (height, weight and BMI calculation) and a clinical interview in order to take note of patient’s clinical history, especially for what concerns the occurrence of previous fractures.

DXA and REMS measurements were performed as already described in Di Paola et al. [15] and briefly summarized here. Anteroposterior DXA scans were performed according to the standard clinical routine procedures. For all the employed DXA devices, i.e. Discovery, Discovery A, Delphi, Delphi C, Horizon W, QDR 4500 SR by Hologic (Waltham, MA, USA), the reference curves adopted to calculate the T-score values were automatically selected by the manufacturer software on the base of patient characteristics and scanned anatomical site. Spinal investigations were carried out with hip and knee flexed at 90°, whereas for femoral examinations the patient’s femur was straight on the table, with the shaft parallel to the vertical edge of the obtained image, and with a 15–25° internal rotation obtained by using a dedicated positioning device. All the DXA medical reports were anonymized and digitally stored for the subsequent analyses. Employed DXA scanners underwent daily quality control and regular maintenance for the whole study period.

REMS scans of lumbar vertebrae and proximal femur were performed using EchoStation echographic devices (Echolight Spa, Lecce, Italy). Data processing methodologies implemented in the REMS approach have been already detailed in previous papers [13,14]. Lumbar scans were performed by moving the echographic convex probe in a transabdominal position along the lumbar vertebrae L1 to L4 according to the audio-video indications provided by the device software EchoStudio (Echolight Spa, Lecce, Italy), whereas proximal femur scans were performed by placing the echographic convex probe parallel to head-neck axis of the femur, in order to visualize the interfaces of femoral head, neck, and trochanter. For each acquisition, the operator had to set transducer focus (in the range 21–100 mm) and scan depth (in the range 60–210 mm) in order to visualize the target bone interface (i.e., vertebral surface or femoral neck) at about halfway through the reconstructed B-mode image depth, where the ultrasound beam focal zone had to be placed. All the REMS medical reports and datasets (including echographic B-mode images and related raw unfiltered signals) were anonymized before starting the subsequent analyses.

A rigorous quality check of all the performed examinations was performed a posteriori in order to guarantee the maximum reliability of the diagnostic outputs [15]. Two experienced operators checked all the medical reports, along with the REMS datasets, in an independent and double-blind configuration in order to identify the possible acquisition errors that might have resulted in inappropriate diagnostic classifications. The guidelines from the International Society for Clinical Densitometry (ISCD) [19] and the indications from recent literature [20] were followed in order to identify DXA errors, which were typically associated with inaccurate patient positioning, analysis pitfalls (e.g., incorrect placement of analysis boxes in the image), presence of artifacts, or mistakes in the registration of demographic characteristics. Concerning REMS errors, they were typically associated with wrong settings of acquisition parameters or with incomplete adherence to the indications provided by the software and/or the user guide.

2.2. Statistical analysis

The distributions of patient characteristics were presented as median and interquartile range (IQR) values. The degree of correlation between DXA and REMS BMD values was quantified through a linear regression analysis, by calculating the slope of the regression line, the Pearson’s correlation coefficient (r) and the coefficient of determination (R²). The agreement between BMD values calculated by DXA and by REMS was assessed by measuring the standard error of the estimate (SEE) and through the Bland-Altman method [21]. The analysis in terms of the diagnostic classification was performed independently for lumbar spine and femoral neck sites, both for DXA and REMS acquisitions. In order to
assess the concordance in 3 diagnostic classes (from here on referred as “diagnostic concordance”) between the two densitometric technologies, each patient was classified as patient with osteoporosis if T-score was \( \leq -2.5 \), patient with osteopenia if \(-2.5 < \text{T-score} < -1.0\) or healthy patient if T-score \( \geq -1.0\). The diagnostic concordance was assessed as the percentage of patients classified in the same diagnostic category (osteoporotic, osteopenic, or healthy) by both DXA and REMS and by the Cohen’s kappa (k). For the evaluation of the ability to discriminate between patients with and without osteoporosis (from here on referred as “diagnostic accuracy”), patients were classified as patient with osteoporosis if T-score was \( \leq -2.5 \) or as patients without osteoporosis otherwise (i.e., T-score \( > -2.5\)). Diagnostic accuracy of the REMS approach was then assessed by assuming DXA results as the gold standard reference and by determining sensitivity and specificity in the discrimination between patients with and without osteoporosis. Positive predictive value (PPV) and negative predictive value (NPV) were also calculated. Moreover, in order to take the borderline cases into account, namely the misclassifications deriving from slight T-score differences around the threshold values of \(-2.5\) and \(-1\), the accuracy and diagnostic agreement parameters were also recalculated accepting a 0.3 tolerance on T-score value of borderline cases, according to an approach already adopted in previous studies [15]. These analyses were presented for 3 different settings of patients: (i) the quality-checked scenario, i.e., considering the couples of DXA and REMS scans that passed the quality check, thus excluding both DXA scans with non-correctable errors and REMS misclassifications due to the wrong selection of depth and/or focus during the ultrasound scan; (ii) the previous dataset stratified by patients’ age; (iii) the “unchecked” scenario, where the DXA errors were still included but the REMS errors were not, in order to ascertain the worse REMS performance with respect to an ideally perfect DXA acquisition.

Moreover, the capability of T-score values to discriminate patients with a previous osteoporotic fracture was assessed in the quality checked scenario by calculating the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve for both DXA- and REMS-measured T-score, and the statistical difference between curves was assessed through the DeLong’s test.

3. Results

3.1. Study population

Overall, 4307 patients were recruited, with 4271 femoral neck scans and 4245 lumbar spine scans performed. With the exclusion of 340 (8.0%) and 408 (9.6%) erroneous DXA reports for femoral neck and lumbar spine, respectively, and of 323 (7.6%) and 373 (8.8%) erroneous REMS scans for femoral neck and lumbar spine, respectively, 3608 femoral neck and 3464 lumbar spine cases, respectively, were subsequently used for the clinical performance analysis. The patients’ characteristics are reported in Table 1. As concerning the contributions by each Institutions participating in the study, the median proportion of enrolled patients was 19.8% (range: 13.0% to 27.0%). The cohorts of Institutions participating in the study, the median proportion of

| Femoral neck, n = 3608 | Lumbar spine, n = 3464 |
|------------------------|------------------------|
| Age (years) | 61.0 | 60.0 |
| Height (cm) | 160.0 | 160.0 |
| Weight (kg) | 62.0 | 62.0 |
| BMI (kg/m²) | 24.12 | 24.12 |
| Age of menopause (years), n = 2129 | 50.0 | 50.0 |
| Age of menopause (years), n = 2123 | 50.0 | 50.0 |

Pearson correlation coefficient \( r = 0.93 \) and corresponding coefficient of determination \( r^2 = 0.86 \). At linear regression analysis, the slope of the regression line was 0.97 and the SEE was 0.044 g/cm². At Bland-Altman analysis, the bias \( \pm 2SD \) values were 0.002 \( \pm 0.088 \) g/cm². The graphical comparison of the BMD values obtained by REMS and DXA is shown in Fig. 1, reporting the scatterplot distribution of REMS BMD against corresponding DXA BMD values (Fig. 1a) and the Bland-Altman plot considering the DXA BMD values as reference (Fig. 1b). Comparing the REMS-based diagnostic classification of patients with without osteoporosis with the DXA-based one considered as reference, the sensitivity and specificity were 90.4% and 95.5%, respectively, which increased to 94.8% and 98.6% when the 0.3 T-score tolerance was accepted. The PPV and NPV were 82.3% and 97.7%, respectively, which reached 94.0% and 98.8% with the 0.3 T-score tolerance. Considering the diagnostic classification in 3 classes (i.e. normal patients, patients with osteopenia, patients with osteoporosis), the concordance was 86.0% with a Cohen’s \( k \) of 0.83. With a 0.3 T-score tolerance, these parameters reached 95.0% and 0.93, respectively.

Similarly, for the lumbar spine cases, the linear correlation between BMD values calculated by DXA and REMS resulted in a Pearson correlation coefficient of 0.94 \( (r^2 = 0.88) \), with the slope of the regression line of 0.90 and the SEE = 0.042 g/cm². At Bland-Altman analysis, the bias \( \pm 2SD \) values resulted \(-0.0002 \pm 0.087 \) g/cm². Evaluating the performance in terms of diagnostic accuracy, a sensitivity of 90.9% and a specificity of 95.1% were obtained (with a 0.3 T-score tolerance, 97.0% and 97.2%, respectively), whereas the PPV and NPV were 85.7% and 97.0% (91.7% and 99.0% with a 0.3 T-score tolerance), respectively. When 3 diagnostic categories were considered, the diagnostic concordance was 86.8% and Cohen’s \( k \) was 0.84 (with a 0.3 T-score tolerance, 94.3% and 0.92, respectively). Fig. 2 reports the comparison of the BMD values obtained by REMS and DXA, represented as scatterplot distribution (Fig. 2a) and Bland-Altman plot (Fig. 2b).

3.2. Stratification by age

The REMS diagnostic performance was investigated also considering subgroups of patients stratified by age, considering younger patients, i.e. between 30 and 50 years, middle-age patients, i.e. between 51 and 70 years, and elderly patients, i.e. between 71 and 90 years. The results are reported in Table 2.

3.2.2. Unchecked “real life” scenario

With the exclusion of the only erroneous DXA reports, namely before a quality check for REMS scans and reports would be performed, the so-called unchecked “real life” scenario was obtained: overall, 3931 femoral neck scans and 3837 lumbar spine scans were analysed.

As concerning the BMD-based analysis, the linear correlation between DXA and REMS resulted in a Pearson correlation coefficient \( r = 0.88 \) and \( r = 0.90 \) for femoral neck and lumbar spine, respectively. The
The slope of the linear regression line was 0.90, with SEE = 0.054 g/cm² for femoral neck, and 0.82 with SEE = 0.052 g/cm² for lumbar spine. At Bland-Altman analysis, the bias ±2SD values were 0.001 ± 0.110 g/cm² and 0.009 ± 0.113 g/cm² for femoral neck and lumbar spine, respectively.

As concerning the T-score based comparison, the sensitivity and specificity obtained by REMS in the classification of patients with/without osteoporosis were 85.5% and 94.5%, respectively, for femoral neck cases, and 89.0% and 94.3%, respectively, for lumbar spine cases. Considering a 0.3 T-score tolerance, the sensitivity and specificity became 91.1% and 98.0%, respectively, for femoral neck, and 95.4% and 97.1%, respectively, for lumbar spine. Considering the 3-class diagnostic classification, the diagnostic concordance was 82.7% and 83.4% for femoral neck and lumbar spine, respectively (92.4% and 91.7%, respectively, when the 0.3 T-score tolerance was considered), with a Cohen’s k of 0.77 and 0.81, respectively (0.89 and 0.91 with a 0.3 T-score tolerance, respectively).

### 3.3. T-score ability in the discrimination of patient groups with or without previous osteoporotic fractures

As shown in Fig. 3, it is evident that both DXA and REMS T-score discriminated significantly between fractured and non-fractured patients: as expected, the T-score values for patients with previous osteoporotic fractures were significantly lower than the corresponding values found for patients without previous osteoporotic fractures. In particular, median femoral T-score value for patients with and without previous osteoporotic fractures were −2.1 (IQR: −2.6 to −1.4) and −1.6 (IQR: −2.3 to −0.9) for DXA, respectively, whereas −2.4 (IQR: −2.8 to −1.6) and −1.6 (IQR: −2.4 to −0.9) for REMS, respectively (p < 0.0001 in both cases); similarly, median lumbar spine T-score value were −2.1 (IQR: −2.7 to −1.3) and −1.6 (IQR: −2.4 to −0.7) for DXA, respectively, whereas −2.3 (IQR: −2.8 to −1.5) and −1.7 (IQR: −2.4 to −0.8) for REMS, respectively (p < 0.0001 in both cases).

The AUCs of the ROC curve obtained by the femoral neck T-score values for the discrimination between groups of patients with and without a previous fragility fracture were 0.631 for DXA and 0.683 for REMS (p < 0.001), whereas, as concerning the lumbar spine dataset, the
Table 2
Analysis stratified by age groups.

| Age groups | Femoral neck | Lumbar spine |
|------------|--------------|--------------|
|            | 30-50 y      | 51-70 y      | 71-90 y      | 30-50 y      | 51-70 y      | 71-90 y      |
| N          | 644          | 2292         | 672          | 945          | 2045         | 474          |
| T-score based analysis |
| Sensitivity [%] | 85.7         | 90.3         | 91.0         | 75.0         | 89.9         | 95.7         |
| Specificity [%]  | 99.8         | 96.0         | 87.6         | 99.8         | 95.2         | 79.2         |
| PPV [%]        | 94.7         | 84.0         | 78.3         | 90.0         | 89.0         | 77.4         |
| NPV [%]        | 99.5         | 97.7         | 95.2         | 99.4         | 95.6         | 95.9         |
| Diagnostic concordance [%] | 92.1         | 84.9         | 83.9         | 91.3         | 85.9         | 81.4         |
| Cohen’s k      | 0.90         | 0.84         | 0.75         | 0.81         | 0.85         | 0.72         |
| 0.3 T-score tol. sensitivity [%] | 90.5         | 93.6         | 97.7         | 87.5         | 96.6         | 99.5         |
| 0.3 T-score tol. specificity [%] | 100.0        | 99.0         | 94.9         | 100.0        | 97.2         | 87.2         |
| 0.3 T-score tol. PPV [%] | 100.0        | 95.8         | 90.4         | 100.0        | 93.7         | 85.9         |
| 0.3 T-score tol. NPV [%] | 99.7         | 98.5         | 98.8         | 99.7         | 98.5         | 99.6         |
| 0.3 T-score tol. diag. conc. [%] | 98.0         | 94.4         | 93.9         | 97.5         | 93.8         | 90.3         |
| 0.3 T-score tol. Cohen’s k | 0.95         | 0.93         | 0.91         | 0.93         | 0.93         | 0.85         |

BMD-based analysis
Slope of the regression line 0.98 0.97 0.86 0.91 0.83 0.79
Person correlation r 0.93 0.91 0.86 0.92 0.92 0.88
$\rho^2$ 0.87 0.82 0.75 0.84 0.84 0.78
SEE [g/cm$^2$] 0.040 0.044 0.043 0.035 0.041 0.041
Bland-Altman bias ±2SD 0.003 ± 0.080 0.005 ± 0.089 −0.010 ± 0.089 0.003 ± 0.072 −0.002 ± 0.091 −0.011 ± 0.092

Fig. 3. Boxplot of the T-score value distributions for patients with and without previous osteoporotic fractures. Femoral (charts above) and lumbar (charts below) distributions are reported, both for DXA (left) and REMS (right).
AUCs of the ROC curve obtained by DXA and REMS T-score values were 0.603 and 0.640 ($p = 0.0002$), respectively.

4. Discussion

With this study, the ability of REMS to assess the BMD and consequently diagnose osteoporosis was evaluated with respect to the current reference densitometric technique, i.e. DXA, in a European multicentre frame. Though the considered cohort of patients was entirely original and unpublished, the design of the study is the same of that presented by Di Paola et al. [15], with the comparison of corresponding DXA and REMS scans, performed on the same patients at the same reference anatomical site. This study represents the extension of the previously cited one, with two main differences: if, on the first study, only Italian patients had been considered, in this case the patient enrolment had been extended at European level, with about the double of the patients enrolled, thus documenting the wide applicability of the methodology; moreover, the involved patients’ age ranges from 30 to 90 years, i.e. far beyond the previously considered patients’ age range between 51 and 70 years, with important implications for a large female population who might benefit from a non-ionizing approach for the diagnosis of osteoporosis and bone health assessment on the axial reference anatomical sites. A specific analysis of the diagnostic accuracy stratifying for different age ranges has also been presented, thus allowing the direct assessment of the performance for younger and elderly women.

The obtained results showed that REMS had a high accuracy in the identification of patients with osteoporosis, with sensitivity and specificity over 90% and diagnostic concordance of about 86% for both the reference anatomical sites. Interestingly, the high impact of the borderline cases, already pointed out in Di Paola et al. [15], has been confirmed: if the cases with DXA and REMS T-score values in the neighbourhood of the transition thresholds between diagnostic classes (i.e. in a $\pm 0.3$ T-score range around the $-2.5$ and $-1$ thresholds) were re-considered and accepted as matching classifications, the sensitivity and specificity increased up to the range 95–99% and the corresponding diagnostic concordance in 3 classes resulted in values over 94%, for both the anatomical sites. The PPV values also increased from about 82–86% to over 91% in case of acceptance of borderline cases for both anatomical sites, whereas NPV values increased from about 97% to values as high as 99%. The reported PPV values, in particular, might be diagnostic concordance in 3 classes resulted in values over 94%, for both the reference anatomical sites. Moreover, REMS measured T-score values over 90%, PPV in the range 82–86% and NPV over 97% for both reference anatomical sites. Therefore, REMS measured T-score values were associated with the occurrence of previous osteoporotic fractures, even at a slightly higher degree than corresponding DXA T-score values.

Further ongoing studies will be dedicated to the assessment of REMS diagnostic performance in a male population and to its employment for the calculation of parameters specifically dedicated to the assessment of bone quality independently from BMD.

CRediT authorship contribution statement

Bernard Cortet: Conceptualization, Methodology, Data curation, Writing - review & editing.
Elaine Dennison: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.
Adolfo Diez-Perez: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.
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Diana Ovejero Crespo: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.
Eugenio Quarta: Conceptualization, Methodology, Investigation, Data curation, Writing - review & editing.
Maria Luisa Brandi: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing - original draft, Supervision.

Declaration of competing interest

BC, ADP and MLB are members of the Echolight Scientific Advisory Board. ED, ML, MM, XN, DOC and EQ have nothing to disclose.

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