REMS technique: future perspectives in an Academic Hospital

Carla Caffarelli
Maria Dea Tomai Pitinca
Valentina Francolini
Mario Alessandri
Stefano Gonnelli

Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy

Address for correspondence:
Carla Caffarelli, MD, PhD
Department of Medicine, Surgery and Neurosciences
University of Siena, Policlinico Le Scotte
Viale Bracci 2
53100 Siena, Italy
Phone: +39 0577 585468; Fax: +39 0577 233446
E-mail: carlacaffarelli@yahoo.it

Summary

Currently, dual X-ray absorptiometry (DXA) is the most widely used method for diagnosing osteoporosis through bone mineral density (BMD) assessments on lumbar spine and proximal femur. An innovative echographic approach for osteoporosis diagnosis, directly applicable on both femoral neck and lumbar spine, has been recently introduced and clinically validated through single-center and multicenter studies. This developed approach has been subsequently defined as Radiofrequency Echographic Multi Spectrometry (REMS). REMS technology arouses the interest of clinicians not only for its characteristics, such as simplicity and repeatability, transportability and absence of ionizing radiation, but also because it can provide information on bone tissue characteristics (elasticity, microstructure) different from the BMD measured by DEXA. Moreover, this technique could also be used in the diagnosis of different metabolic bone diseases, in patients with corticosteroid-induced osteoporosis, in diabetics, or in women treated with aromatase inhibitors, conditions in which the assessment of BMD underestimates the fracture risk.
Furthermore, the absence of ionizing radiation represents a valid possibility of using REMS echography to assess bone mineral status in children.

KEY WORDS: Radiofrequency Echographic Multi Spectrometry (REMS); osteoporosis diagnosis; bone quality.

Introduction

Osteoporosis is a systemic skeletal disorder characterized by decreased bone mass and qualitative alterations (macro- and micro-architecture, bone material properties) associated with increased fracture risk (1). Fractures related to osteoporosis are currently considered a public health problem since they significantly increase the morbidity and mortality of affected patients, especially in the case of hip fracture (2). The diagnosis of osteoporosis is currently established by measurements of bone mineral density (BMD) and Dual X-ray Absorptiometry (DXA) of proximal femur and lumbar spine is the reference technology used to establish or confirm a diagnosis of osteoporosis. According to the World Health Organization (WHO) diagnostic classification, osteoporosis is identified when BMD at the hip or lumbar spine is less than 2.5 standard deviations (SDs) below the mean value of young adult reference population (3).
However, the employment of ionizing radiation, with associated risks and costs, makes DXA not suitable for population mass screenings; moreover, DXA measurements are available only in secondary care settings and they are actually under-utilized in the majority of European countries, with the main reasons including a limited number of densitometers, restrictions in personnel permitted to perform scans and low awareness of usefulness of BMD testing. Recent literature has also pointed out that clinical routine DXA scans are often performed with a poor adherence to the guidelines of the International Society for Clinical Densitometry (ISCD), resulting in the fact that a high percentage of DXA reports present operator-dependent errors (4). It has been known for many years that most fragility fractures occur in subjects classified as “normal” or “osteopenic” on the basis of WHO criteria; in fact, although BMD is an important predictor of bone strength, additional parameters, such as tissue intrinsic material properties and bone microarchitecture, should be evaluated in order to define bone strength more accurately.
For this reason, the last two decades have seen increased interest in using Quantitative Ultrasound (QUS) techniques for the identification of subjects at increased risk of osteoporosis and fragility fractures. In fact, several studies have reported that QUS parameters may reflect not only BMD but also other qualitative properties of bone (e.g., elasticity and microarchitecture) that are strictly related to strength. Even though the correlation between QUS parameters and BMD measurements is moderate, several studies have shown that ultrasound-derived parameters, namely, speed of sound (SOS) and Broadband Ultrasound Attenuation (BUA) at calcaneous, are not inferior to lumbar or hip DXA in predicting the risk of osteoporotic fractures (hip and spine), both in postmenopausal women and in elderly men (5, 6). Moreover, QUS may be useful when lumbar or hip DXA is not feasible, and may be recommended for epidemiological studies and

for first line screening, given its relatively low cost, portability and lack of radiation exposure. However, the heterogeneity of ultrasound machines, which provide values that are not always comparable, is an important limitation of QUS (6). Established QUS methods are applicable only on peripheral bone sites and their limited diagnostic power derives from the absence of clear relationships with the health status of hip and/or spine, which actually represent the fracture sites carrying the largest costs and the most severe reductions in patient quality of life. Considering that site-matched correlations between BMD and QUS parameters are typically better than the corresponding ones obtained from different sites, proximal femur has become the target of several experimental studies aimed at translating the measurement of peripheral QUS parameters to the femoral site (7). On the other hand, at present, the clinical translation of the few QUS methods working on the axial sites was prevented either by the limited accuracy or by the bulkiness and complexity of the employed devices (8).

Radiofrequency Echographic Multi Spectrometry (REMS)

An innovative echographic approach for osteoporosis diagnosis, directly applicable on both femoral neck and lumbar spine, has been recently introduced and clinically validated through single-center and multicenter studies. This developed approach has been subsequently defined as Radiofrequency Echographic Multi Spectrometry (REMS). The main output parameter of this fully non-ionizing technique is BMD_{US}, a diagnostic index expressed as grams/cm^2, which is measured directly on lumbar vertebrae or proximal femur and has shown significant correlations with the corresponding BMD values and good agreement levels with DXA-based diagnoses assumed as the gold standard reference (9, 10).
In particular, the REMS technology also gives an innovative diagnostic parameter, called Fragility Score (FS), which investigates bone quality and provides risk estimation fracture independently of BMD by the analysis of bone micro-architecture. The FS is a dimensionless parameter which derives from spectral analysis and dedicated statistics realized by an algorithm which compares the spectral characteristics of raw radiofrequency (RF) signals acquired during a lumbar ultrasound scan, with appropriate models of “frail” or “non-frail” bone structures, previously obtained from data collected from patients with or without fragility fractures (11, 12).
Therefore, Fragility Score (FS) investigates bone quality (by analyzing bone micro-architecture) and provides fracture risk estimates independently of BMD. Some studies have shown a high correlation coefficient between the fracture probabilities calculated by FRAX® and FS ($r = 0.72$, $p < 0.001$) in case the estimation of the value of FRAX® also takes into account the T-score of the femoral neck.

Novel approaches REMS technique

The availability of FS obtained by REMS technology may represent a valid support in the study of all those diseases involving bone tissue in which the sole determination of bone mass does not seem to be sufficient in determining bone tissue impairment and the fragility fracture risk.

Therefore, this technique arouses the interest of clinicians not only for its characteristics, such as simplicity and repeatability, transportability and absence of ionizing radiation, but also because it can provide information on bone tissue characteristics (elasticity, microstructure) different from the bone mineral density, commonly measured by DEXA techniques (Table 1). Moreover, this technique could also be used in the diagnosis of different metabolic bone diseases such as osteomalacia, hyperparathyroidism and renal osteodystrophy. REMS could also be used in patients with corticosteroid-induced osteoporosis, in diabetics, or in women treated with aromatase inhibitors, conditions in which the assessment of BMD underestimates the fracture risk.

Diabetes

In particular, the patients with type 2 diabetes (T2D) present a higher fracture risk than nondiabetic subjects, despite similar or greater BMD measurements (13, 14). In fact, many studies have reported that in T2D patients poor bone quality rather than a decreased bone density may play a crucial role in determining the risk of fragility fractures. In a previous study we found that T2D patients presented reduced values of trabecular bone score (TBS) and higher values of BMD with respect to control subjects (15). On the basis of these data, an epidemiological multicenter study is going to start in order to clarify whether REMS Ecography is able to assess the alterations in bone quality in T2D patients and also to predict the fracture risk.

Monitoring of drugs associated to osteoporosis and fragility fractures

REMS technique has also a huge potential to be employed for therapeutic monitoring purposes, thanks to its very good precision and inter-operator repeatability coupled with the well-known advantages of an ultrasound-based technique (absence of ionizing radiation, low costs, accessibility, etc.). Moreover, speed of the scan together with complete automaticity of data processing, makes these investigations absolutely compatible with the needs of the clinical routine. In fact, the availability of a REMS echographic device in the visiting room may facilitate the diagnostic procedures with a substantial saving in time.
Glucocorticoid-induced bone loss is an early event (in the first weeks of treatment), and is more pronounced during the first 6 to 12 months of treatment, mainly affecting trabecular bone (particularly, vertebral fractures occur early after initiation of steroid therapy). Thereafter, there is a reduction in osteoclast-mediated bone resorption but inhibition of bone for-

Table 1- Strengths of REMS technique.

• Easily and fast measurements
• Portable
• Low cost
• Lack of radiation exposure
• Quantitative and qualitative information on bone status
• Measurements on fracture sites (proximal femur and lumbar spine)
• High reproducibility

mation is maintained: bone loss is slower but constant, also involving cortical bone. It is important to remember that fracture risk in glucocorticoid-induced osteoporosis is much higher as compared to that expected based on DXA BMD values, and rapidly decreases after treatment discontinuation (16, 17).

Treatment with an aromatase inhibitor (AI) for 5 years as upfront monotherapy or after tamoxifen therapy is the treatment of choice for hormone-receptor-positive early breast cancer in postmenopausal women. Extending treatment with an AI to 10 years may further reduce the risk of breast-cancer recurrence. It is well known that adjuvant hormonal therapy with AIs or tamoxifene + LHRH analogues in women with breast cancer leads to an accelerated bone loss and rapidly increases fracture risk. Moreover, fracture risk reduction (with denosumab or bisphosphonates) is independent of BMD values at initiation of antiresorptive therapy. Also androgen deprivation induced by GnRH agonists and/or antiandrogens in men with prostate cancer induces a rapid increase in fragility fracture risk (18, 19).

In these patients BMD by DXA has been reported to underestimate fracture risk. Further studies are needed to evaluate whether REMS technique could improve the therapeutic monitoring of drugs associated to increased fracture risk through short-term follow-ups.

Special categories of patients

The absence of ionizing radiation represents a valid possibility of using REMS Echography in childhood. In the latter field, moreover, the bone density of DXA has considerable limitations due to both the use of ionizing radiation and to technical difficulties in executing the exams in some subgroups of pediatric patients with significant skeletal involvement (20).

Because of transportability the REMS device can be used directly on the patient's bed, and this could represent an excellent method for assessing the bone status even in subjects with a recent osteoporotic hip fracture. In elderly patients with skeletal fragility an adequate treatment markedly reduces the risk of re-fracture, with a consequent reduction in mortality, disability and hospital re-admissions. However, at present, only 20% of hip fracture patients are discharged after surgery with treatments for osteoporosis also because of practical difficulties in carrying-out a DXA examination during their stay in hospital (21).

In conclusions, REMS technique, thanks to its good precision and inter-operator repeatability, may be used for diagnostic and therapeutic monitoring purposes. Further studies are warranted in order to explore the possibility of obtaining clinically relevant information on bone quality.

Conflict of interest

Carla Caffarelli, Maria Dea Tomai Pitinca, Valentina Francolini, Mario Alessandri, Gonnelli Stefano declare that they have no conflict of interest.

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