Radiofrequency Echographic Multi-Spectrometry in the Diagnosis of Metabolic Bone Disease

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Abstract

Dual-energy X-ray absorptiometry (DXA) and bone mineral density (BMD) pose several limitations in some patient categories, such as pregnant women and young people. This review article explores whether the innovative radiofrequency echographic multi-spectrometry (REMS) technology is beneficial for assessing the bone condition of various patient groups. Common consequences in patients with acromegalia, prostate cancer undergoing hormone therapy, osteogenesis imperfecta, anorexia nervosa, and in a peritoneal dialysis setting include decreased BMD and an increased risk of fragility fracture.

DXA is currently regarded as the gold standard for BMD assessment. However, using the DXA technique has several drawbacks in a young patient who requires repeated BMD tests because it uses ionizing radiation. Because of its precision and consistency, the REMS technique may be a valuable tool to assess changes in bone condition in patients of all ages, particularly in female patients who are fertile or who are pregnant or nursing.

Keywords

- bone mineral density
- osteoporosis
- radiofrequency echographic multi-spectrometry
- bone health status

The primary cause of fractures that occur in adults > 50 years of age because of nontraumatic injuries or low- to medium-energy traumas, commonly referred to as fragility fractures, is osteoporosis, a metabolic bone disease marked by low bone mass and changes in the macro- and microarchitecture of the skeletal tissue. The idea of this illness has changed over the years from first regarded as an unavoidable side effect of aging to acknowledging it as a serious condition that can be treated.

The main objective of better osteoporosis care, in terms of early diagnosis and therapy monitoring, is the prevention of incident fragility fractures and their possible aftereffects of comorbidities, impairments, and the accompanying higher relative mortality. During wellness visits with postmenopausal women, primary care providers should regularly integrate specific screening strategies for bone health assessment. Screening should happen earlier if specific conditions are present, such as the diagnosis of a fracture, especially if it is not of traumatic origin. Risk factors for these conditions include acromegalia, prostate cancer under hormone therapy, osteogenesis imperfecta (OI), anorexia nervosa (AN), premature menopause, chronic glucocorticoid therapy, low body weight, family history of osteoporotic fractures, diseases affecting bone metabolism, or excessive daily alcohol consumption, among several other conditions.[1,2]

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Bone mineral density (BMD), defined as the amount of bone mass per unit of area or volume (areal BMD [aBMD], expressed as g/cm^2), is the key to diagnosing osteoporosis. A detector measures the amount of attenuation of an incident X-ray that has passed through the patient's tissues. Dual-energy X-ray absorptiometry (DXA), based on bone X-ray absorptiometry, is the clinical reference among the variety of imaging techniques currently available for the assessment of BMD.[3]

Based on the examination of ultrasonographic (US) signal backscattering, radiofrequency echographic multi-spectrometry (REMS), a relatively new technology, analyzes bone amount and quality using a nonionizing method.[4]

The National Health and Nutrition Examination Survey is used as a normative reference database to derive the corresponding T-score and Z-score values. The BMD is determined using sophisticated comparisons of the patient's specific spectrum of the target bone against a proprietary database of reference US spectral models. Multiple nationwide studies have supported this technique, with each study focusing on a different age range. In a large European female population spanning a wide age range, a review article sought to evaluate the diagnostic accuracy of the REMS technology compared with DXA, with a particular emphasis on comparing the capacity of the two technologies to identify subjects with prior osteoporotic fractures.[5]

Bone Metabolism and Increased Risk of Fracture

As part of the continuous cellular metabolism that takes place in human bone cells, stromal cells, erythropoietic cells from the bone marrow, and other bone cells interact with one another to remodel and regenerate bone. An essential part in bone metabolism is played by osteoclasts and osteoblasts; the processes involved in bone metabolism are not independent; rather, they work in concert. In addition to being the birthplace of hemopoiesis, bone is essential to maintain the balance of minerals like calcium and phosphate and acts as a storehouse for growth nutrients. About 20% of the skeleton is made up of trabecular bone; the remaining 80% is cortical bone. Haversian systems, a branching network of cylindrical osteons, make up the dense cortical bone.[6]

The packets known as osteons that make up trabecular bone are organized in a honeycomb arrangement. Bone marrow, the nonmineralized portion of bone, is made up of hematopoietic cells (red marrow) and adipocytes (yellow marrow). Except for joints, the periosteum covers the outside cortical surface of bones; the endosteum covers the interior surface. Although the endosteum is a membrane structure and the periosteum is a fibrous connective tissue, both include blood vessels, osteoblasts, and osteoclasts.[7]

Osteocytes, osteoblasts, and osteoclasts are the main cellular components of bone, encased in a mineralized extracellular matrix. Osteoblasts release calcium and phosphate-containing vesicles to synthesize bone matrix and control mineralization. Collagenous proteins, primarily type I collagen, and bone minerals, primarily hydroxyapatite, make up the mineralized matrix of bone. This matrix envelops and subsumes osteoblasts that subsequently develop into osteocytes. Osteocytes and the cells that line the surface of the bone form a biochemical network. Their primary job is to communicate with the network of osteocytes and osteoblasts to convert mechanical stress into a biological reaction. The only cells with the ability to resorb bone are osteoclasts, essential to the remodeling of bone. Throughout life, the dynamic structure of bones grows, changes, and is remodeled in response to mechanical stresses, metabolic processes, and hormonal effects. Units of old bone are continually removed throughout the process of bone remodeling, and a new proteinaceous matrix is added. This matrix is then mineralized. This equilibrium can be upset by several factors, such as rheumatoid arthritis or changes in hormone levels in osteoporosis.

The Fracture Risk Assessment Tool (FRAX) increases when this equilibrium is skewed in favor of bone loss in osteoporosis, resulting in a decrease in bone mass with thinning trabeculae and increased porosity of cortical bone.

Acquisition Method

REMS technology assesses bone health status by performing a simple echographic scan of the spine and femur, by placing a probe on the abdomen (►**Fig. 1a**) or hip (►**Fig. 1b**).

REMS scans were performed using a dedicated echographic instrument (EchoStation, Echolight Spa, Lecce, Italy) equipped with a convex transducer operating at the nominal frequency of 3.5 MHz and following the manufacturer's recommendations. An echographic scan is performed by placing the echographic transducer in a transabdominal position to visualize L1–L4 lumbar vertebrae, by moving the probe according to audible indications provided by the device software. Each lumbar scan lasts 80 s (20 s per vertebra).

For femoral investigations, the echographic transducer is placed parallel to the head-neck axis of the femur, to visualize the femoral head, neck, and trochanter. The femoral scan lasts only 40 s. Immediately after the scan, automatic processing of the acquired signals allows us to identify and analyze the target bone structure and the internal region of interest. Finally, the selected measured data are synthesized into a patient-specific spectrum of the targeted bone, which is advanced compared with sex, age, site, and body mass index (BMI)-matched reference spectral models collected from a dedicated database.

Basic Principle

The basic principle of REMS is based on the analysis of native raw unfiltered US signals, acquired during the echographic scan of lumbar vertebrae and/or the femoral neck.[8] The analysis of native unfiltered US signals allows us to retain the maximum information about the characteristics of the investigated tissues that are normally filtered out during the conventional process of B-mode image reconstruction. Bone health status is assessed through the comparison of the spectra profile of the patient, with the previously derived reference spectral model's representative of osteoporotic and healthy conditions.

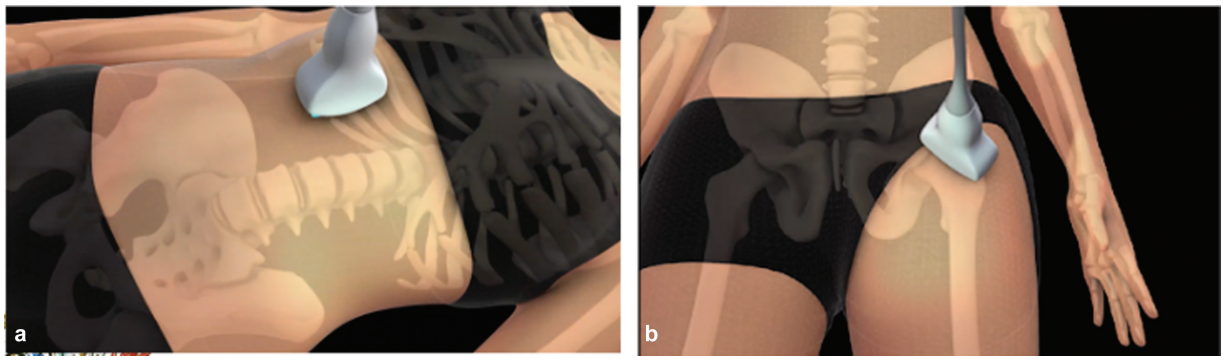

Fig. 1 (**a**) Ultrasonography (US) acquisition on an axial anatomical site of the lumbar vertebrae. (**b**) US acquisition on an axial anatomical site of the femoral neck.

This process allows us to estimate BMD, T-score, and Z-score.[9] Once the BMD, T-score, and Z-score are obtained, it is possible to classify the patient as healthy, osteopenic, or osteoporotic. In addition, the analysis of single scan line spectra allows the automatic exclusion of signals corresponding to artifacts, such as calcifications or osteophytes, thanks to the identification of unexpected spectral features.

A Japanese population cross-sectional study showed how the REMS can overcome the effects of structural internal artifacts and evaluate bone fragility accurately.[10,11] The authors evaluated BMD and T-scores using DXA and REMS and compared the results. REMS reported notably lower average lumbar spine, femoral neck, and total proximal femur BMD and T-scores than DXA. Internal artifacts, including vertebral fractures and abdominal aortic calcifications, are known to directly impact the lumbar spine BMD measurements obtained via DXA.[12]

Consistent with expectations, the greatest discrepancies were observed in lumbar spine BMD readings, where REMS registered a more accurate BMD and a T-score, whereas DXA reported an underestimated BMD value and a T-score; these differences were statistically significant ($P < 0.001$). This study demonstrates that REMS may provide a more accurate measurement of BMD than DXA that overestimates BMD due to factors such as vertebral abnormalities, abdominal aortic calcification, and diabetes mellitus (DM). As a result, REMS may provide a more precise assessment of bone fragility, demonstrating its potential as an important clinical practice tool.[13]

In 2020, a further study assessed whether the use of REMS technology would aid the diagnosis of osteoporosis in subjects with apparent increased BMD, assessed by DXA.[14] The study was based on a cohort of 159 white women aged 50 to 80 years, postmenopausal status, BMI between 18.5 and 39.9 kg/m^2, presence of moderate/severe vertebral fractures or osteoarthritis (OA) at the lumbar spine, as confirmed by radiography taken in the previous 6 months. The patients previously treated with anti-osteoporosis drugs, except calcium and vitamin D supplements, and those who had an illness (e.g., cancer, multiple myeloma, hyperparathyroidism, etc.) or were receiving therapies able to influence bone metabolism (glitazones, glucocorticoids, anticonvulsants, etc.) were excluded.[15]

OA and vertebral fractures at the lumbar spine resulted in an overestimation of BMD, and REMS represents an innovative diagnostic tool that appears to be able to investigate bone quality and provide an estimate of fracture risk independent of BMD.[16]

All radiologic documentation was reviewed by two of the authors with specific expertise. All lumbar radiographs were analyzed for the presence of any vertebral fracture using Genant's technique. Furthermore, the presence of osteophytes was assessed on lumbar spine X-rays using the Kellgren-Lawrence grading method. As expected, the values of T-score BMD-LS by DXA were significantly higher ($P < 0.05$) concerning bone mineral density-lumbar spine (BMD-LS) by REMS. Instead, at both femoral sites, the values of T-score by DXA were slightly higher only for those assessed by the REMS technique.[17]

Moreover, when considering DXA measurements, the T-score at LS was higher than those at both femoral neck (FN) and total hip (TH). This work offers the first report on the effectiveness of REMS in enhancing the diagnosis of osteoporosis when lumbar spine BMD by DXA is hampered by artifacts caused by the presence of fragility fractures or OA changes.[18,19]

The gold standard for determining BMD is DXA, a crucial step in determining fracture risk. However, DXA is not without limits. DXA's two-dimensional scan images (i.e., aBMD) yield only quantitative information; no qualitative three-dimensional information regarding bone structure can be collected. According to a 2020 study, REMS technology may help diagnose osteoporosis more accurately in individuals whose lumbar spine OA or vertebral fractures appear to have increased BMD.

Nevertheless, further studies are needed to confirm these preliminary data and to establish the usefulness of REMS for better assessment of fracture risk in patients with overestimated BMD by DXA at the lumbar spine.

Discussion

The recently developed REMS method uses US to measure BMD at the spinal-level lumbar and proximal femur. REMS was recently validated by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and

Musculoskeletal Diseases. In October 2021, REMS was integrated into the Health Ministry Guidelines that concern the diagnosis and care of fractures, approved by the Italian Health Ministry and the most important scientific clinical bodies. National and European multicenter studies have demonstrated the correlation of REMS with DXA in primary osteoporosis.[20]

REMS technology was developed to overcome the limitations of current approaches such as the standard DXA and peripheral quantitative ultrasonography (QUS) technique. Whereas DXA is based on the use of ionizing radiation for the investigation of axial reference sites of the skeleton, the QUS technique is a radiation-free approach designed to the investigate at the peripheral skeletal sites such as radius, tibia, calcaneus, and phalanges. REMS is a unique and patented technology, the first radiation-free technique directly applied to anatomical reference sites for osteoporosis diagnosis, such as the spine and femur, the same sites investigated by conventional DXA.[21]

The REMS was found to be even more sensitive than DXA, especially in older adult patients, thanks to the intrinsic possibility in the method's software to eliminate the lumbar extraosseous factors that generally interfere with the measurement of BMD (g/cm^2) with the DXA method. The standard method for measuring bone mass is bone densitometry with DXA methodology. Bone mineral content is projected onto the area of the bone segment under examination to determine a parameter known as BMD. Thus BMD serves as a kind of surrogate for actual volumetric density. Nevertheless, a wealth of scientific data spanning over 40 years indicates that BMD as determined by DXA is the primary indicator of fragility fracture risk. Research indicates that the risk of fracture at each site rises 1.5 to 3 times for every standard deviation (SD) ($\sim$ 10%) decrease in BMD.

Densitometry is performed at the proximal lumbar spine because it is more predictive of fracture risk if the BMD measurement is site specific, so it is done at the lumbar spine, proximal femur, total hip, and neck, the sites most frequently affected by fragility fractures. Furthermore, at least 50% of the bone at these locations is spongy, which is more easily weakened by osteoporosis than cortical bone. Spinal BMD evaluation may be affected by extra- or paravertebral X-ray attenuating abnormalities (e.g., arthritic osteophytes, aortic calcifications) or vertebral fractures that should be ruled out when determining mean BMD. Valid lumbar BMD reporting requires that at least two neighboring vertebrae be evaluated. These factors make measuring the BMD of the femur neck more indicative of fracture risk, particularly after 65 years of age. BMD may need to be measured at the radius level in certain situations, considering the value found at the distal third (or 33%) of the bone examined.[22]

These situations include primary hyperparathyroidism (cortical bone), obesity subjects (weight over densitometry table capacity), spinal column (arthrosis, fractures), and femur (bilateral prosthesis) that cannot be evaluated. Densitometric reporting of osteoporosis is based on a comparison between the average BMD value of healthy adults of the same race and sex at the age of peak bone mass (T-score) and the BMD value of the subject under examination, expressed in SD. According to the World Health Organization (WHO), a reduction in BMD of at least 2.5 SD compared with the average result of healthy young adults (T-score $< -$ 2.5) indicates a condition of "densitometric osteoporosis." The diagnosis of "osteoporosis disease" cannot be made based on densitometric reporting alone; it always requires clinical evaluation as well. By agreement, a T-score $< -$ 2.5 is diagnostic of osteoporosis, and a T-score < -1.0 but $> -$ 2.5 is diagnostic of osteopenia.[23]

The lowest T-score value among the three sites (spine, total femur, or femoral neck) should be considered for densitometric classification. Densitometric reporting according to the T-score is used for postmenopausal women and men $>$ 50 years of age. In contrast, densitometric reporting for women of childbearing age and men $<$ 50 years of age is done by comparing the measured BMD value with the average value of subjects of the same age and sex (Z-score). A BMD value equal to a Z-score $< -$ 2 SD indicates a condition of "reduced bone density for age"; a BMD $>$ 2 SD of Z-score value indicates normal bone density for age.

The densitometer's management computer can be equipped with specialized software that assesses a parameter associated with the qualitative aspect of bone strength. This software helps conclude the assessment of patients who have bone fragility and is known as the Trabecular Bone Score (TBS). Using this software, the lumbar spine DXA scan's degree of pixel distribution inhomogeneity is assessed, indirectly revealing trabecular microarchitecture. According to the many studies that have been published to date, TBS is a predictor of fracture risk independent of BMD; in contrast, it has been demonstrated that TBS is more helpful in secondary osteoporosis, where there is a predominance of qualitative bone alteration. TBS has been incorporated into FRAX as a result.[24]

Treatment efficacy can be tracked by evaluating changes in bone mass over time by subsequent DXA densitometry exams. The so-called least significant change (LSC), or the smallest alteration that the technique used can detect and cannot be attributed to measurement error, must be considered in these modifications. Densitometric evaluation is normally warranted only after 18 months because the LSC can vary from 2 to 4% depending on the measuring site and procedure. The gap between densitometric exams may be as brief as 12 months in certain cases of extremely bone-reconstructive medications (such as romosozumab) or disorders that are strongly osteopenizing (e.g., high-dose corticosteroid therapy).

It is strongly recommended to perform densitometric controls with the same device and possibly at the same center to have a more accurate comparison, relying on, however, centers undergoing quality control. Subsequent studies have demonstrated that REMS, compared with DXA, has a greater predictive capacity for fracture risk in patients with secondary skeletal fragility (nephropathic, diabetic), using a new index, the "fragility score." The absence of radiation and the transportability of the REMS allows the evaluation of BMD without any risk in children, during pregnancy, in screening, and in bedridden patients.

Changing ideas regarding the pathophysiology of osteoporosis are reflected in the changing definitions of the disorder as noted in the National Institutes of Health consensus conferences held in 1984 and again in 2001. In 1984, it was defined as follows: "Primary osteoporosis is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recognizable causes of bone loss." In 2001 it was changed to "Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality."[25]

A complication of osteoporosis is the occurrence of fracture by minor trauma acting on poorly resistant bone. The most common sites of osteoporosis fractures are the femur, vertebrae, distal radius, and proximal humerus: 2.7 million osteoporosis fractures in 2017 in EU6 (France, Germany, Italy, Spain, Great Britain, Sweden), of which two thirds were in women. Long bone fractures are easily diagnosed because they cause pain, so a traditional radiologic examination of the affected segment is performed immediately to ascertain the presence of the fracture. In contrast, vertebral fragility fractures if mild are often misdiagnosed, both because they are asymptomatic and because they present as deformities of the vertebral body by reduction of one of its heights beyond a certain threshold value (20%) in the absence of an obvious fracture, as defined by Genant's semiquantitative method: but not all vertebral deformities are fractures.

Application

It seems clear that the fields of application of REMS can be manifold, and thus it can be a valuable aid in managing a variety of osteoporosis-related diseases, such as in the follow-up of cancer patients undergoing hormone therapy or peritoneal dialysis, patients with type 2 DM, in OI, or even in AN. Another field of application of no small importance is pregnant women, due to its radiation-free approach.

Type 2 Diabetes Mellitus

The prevalence of type 2 DM is increasing worldwide, especially because of our aging society, sedentary lifestyle, and the obesity epidemic. Therefore, DM and its complications represent a major cause of morbidity and mortality and result in increased economic burden.[26]

Besides the well-known renal and cardiovascular complications, the increased risk for fragility fractures has recently been recognized as an important complication of type 2 DM. Despite the frequently retained BMD, a growing body of data has linked type 2 DM with skeletal fragility.[27]

Given that individuals with type 2 DM have poorer postfracture outcomes, including mortality, bone treatment in this extremely susceptible population needs to be carefully evaluated. There are concerns over the best way to diagnose and treat bone health in people with the disease because existing fracture risk calculators do not accurately estimate fracture risk in this population, and there are insufficient dedicated randomized controlled studies that determine the best course of action for these patients. Several meta-analyses have reported that type 2 DM patients not only have a 1.5- to 3-fold higher fracture risk, particularly for hip fractures, but also for all nonvertebral humerus, wrist, and ankle fractures, where the evidence for vertebral fractures was lower. However, several studies have reported that type 2 DM patients have a higher risk of vertebral fractures and that this risk is particularly elevated in postmenopausal women with DM. In 2020, a study was conducted with a cohort of 90 consecutive white women with type 2 DM between 50 and 80 years of age, age at diagnosis >30 years, in postmenopausal status, with BMI between 18.5 and 39.9 kg/m^2, and glycated hemoglobin values $<8.5\%$. Patients previously treated with anti-osteoporosis drugs, except for calcium and vitamin D, and those patients with diseases (e.g., cancer, multiple myeloma, hyperparathyroidism, etc.) or who had received therapies that can alter bone metabolism (glitazones, glucocorticoids, etc.) were excluded from the study.[28]

All patients underwent BMD measurement at the lumbar spine (LS-BMD), femoral neck (FN-BMD), and total hip (TH-BMD) using both DXA and REMS, based on the values provided by the WHO about the definition of osteoporosis (T value <-2.5) and osteopenia ($-2.5>$ T value <-1.0). The study included subjects with insignificant differences between the two groups (postmenopausal women with type 2 DM and healthy control group) in terms of age, height, biochemical and hormonal parameters, and dietary factors. As expected, BMI was significantly higher ($P<0.05$) in women with type 2 DM than in the healthy control group. DXA measurements (LS-BMD, FN-BMD, and TH-BMD) were all higher in type 2 DM than in non–type 2 DM women, but the differences reached statistical significance ($P<0.01$) only for LS-BMD and TH-BMD.[29]

Instead, all REMS values were lower in type 2 DM than in non–type 2 DM women, although the differences were not statistically significant. Of course, this study has limitations because the measurement of glycated hemoglobin was carried out only at the beginning of the study, and therefore it is not possible to exclude that there have been changes in glycemia in the following months and finally that the study group had some peculiar characteristics (postmenopausal women with long-lasting DM). This therefore makes the results of the study not reproducible for the diabetic population having different characteristics.

Menopause

Because osteoporosis is the main risk factor for fractures, it is clinically significant. Osteoporotic fractures of the forearms, hips, and spine are linked to physical deformity, lower quality of life, loss of independence, chronic discomfort, and limitations in walking.[30,31]

Menopause with all its hormonal changes plays a major role in altering the metabolic structure of bone tissue. One of the most prevalent bone illnesses is primary osteoporosis, further subdivided into senile osteoporosis and postmenopausal osteoporosis.

Although fragility fractures are the gold standard for diagnosing osteoporosis, DXA measurement of BMD can reliably identify osteoporosis before fracture, and the REMS technique also has the potential to become a gold standard method in such a screening process.[32]

Women may be screened for osteoporosis based on their weight and age. Exercise has a modest positive impact on increases in bone mass, strengthens muscles, and can assist in reducing falls.[33]

Women should ensure they obtain enough calcium and vitamin D. Menopausal hormone treatment (MHT) is recommended for women < 50 years of age because it effectively reduces osteoporosis and fractures. MHT or tibolone may be prescribed to women < 60 years of age, particularly if they have genitourinary or vasomotor symptoms. Then, persons > 60 years may be excluded from receiving risedronate or bisphosphonates.[34,35]

Cancer Patients Undergoing Hormonal Therapies

In recent years, people with cancer have had a higher survival rate, which unfortunately coincides with an increase in the skeletal effects of cancer treatment directly proportional to increasing age. This is especially true for those patients who are receiving hormonal therapies, as in the case of breast and prostate cancer, for example. Therefore, the high average age of patients with these malignancies, together with the natural propensity of older adults toward the development of osteoporosis and the wide use of therapeutic agents in these cancers that negatively impact bone health, lead to an earlier state of osteopenia/osteoporosis.[36]

Various therapies used in cancer treatment and prevention can cause a decrease in BMD and an increased risk of debilitating fractures, even in the absence of bone metastases. Aging is both an underlying risk factor in the development of osteoporosis and bone fractures and a predictor of poor outcomes after fracture. Bone loss in breast or prostate cancer patients could be caused by several different processes. Cytotoxic chemotherapy may have long-term toxic consequences on bones. Chemotherapy and endocrine therapy can induce hypogonadism, leading to an increased rate of bone loss, so the risk of skeletal events in older adults due to cancer therapy should be evaluated by all physicians.

We carried out a study to assess the status of bone health by REMS technology in prostate cancer patients, to analyze the prevalence of osteoporosis during androgen deprivation therapy (ADT). In patients with prostate cancer, bone health impairment is observed, a frequent and harmful consequence of the high bone tropism induced by prostate cancer cells; this is also exacerbated by prolonged treatment with ADT, leading to bone matrix loss (with a loss rate of 4.6% per year, up to ~ 10 times the normal loss) and the consequent increased risk of fractures. This patient category needs to undergo constant monitoring of bone health status.

This study aims to assess the impact of prostate cancer on BMD, thanks to REMS technology measurement, in a group of 35 white men with prostate cancer and a group of healthy controls matched for sex, ethnicity, age, and BMI, who underwent REMS scans on the lumbar spine. The patients with prostate cancer showed a significant reduction of BMD values compared with the healthy control with a difference equal to $0.05 \pm 0.10\,g/cm^2$. The obtained results confirm, as expected, a significant reduction of lumbar BMD in patients with prostate cancer measured with REMS, due to the negative impact of prostate cancer and the ADT on bone health that increase bone turnover and the risk of fractures.

Anorexia Nervosa

AN is a psychiatric condition defined by a low body weight because of self-induced malnutrition. According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), a subject diagnosed with AN must meet all the following conditions: restriction of food intake leading to weight loss or a failure to gain weight resulting in a "significantly low body weight" of what would be expected for someone's age, sex, and height; intense fear of becoming fat or gaining weight; and disturbance in body image.[37]

AN is common among adolescent and young adult women. In Italy, the lifetime prevalence of AN in the female population > 18 years of age is $\sim 0.9\%$. Endocrine changes include hypothalamic amenorrhea, a nutritionally acquired growth hormone resistance with low insulinlike growth factor (IGF)-1), relative hypercortisolemia, low leptin, insulin, amylin, and oxytocin, and high peptide YY (PYY) and adiponectin. All these alterations have a detrimental effect on bone; in fact, low BMD is a hallmark of AN and should be taken very seriously. AN affects both cortical and trabecular bone; in particular, the rapid loss of trabecular bone reflects the severe effects of estrogenic deprivation. Reduced BMD and increased risk of fragility fracture are the common and the most relevant complications of AN.[38]

BMD by DXA presents several limits in subjects with AN and is most important in adolescence, a time when bone accrual peaks. In the literature, it is possible to find an original article that aims to assess the state of the bone in young women with AN. The study group was represented by a cohort of 50 subjects with restrictive AN and 30 healthy controls.[39]

The population enrolled in the study included young women aged < 18 years, BMI $< 18\,kg/m^{2,}$, and a diagnosis of restrictive AN as defined by DSM-5. The control group included 30 normal-weight healthy adolescents and young women aged < 18 years with BMI $< 25\,kg/m^2$. All of the controls reported no history of eating disorders and normal menstrual cycles. All the subjects previously treated with anti-osteoporosis drugs, except calcium and vitamin D supplements, and those who had an illness (cancer, multiple myeloma, hyperparathyroidism, etc.) or were receiving therapies able to influence bone metabolism were excluded.

There were no significant differences between the two groups for age, height, biochemical parameters, parathyroid hormone, and 25-hydroxyvitaminD (25OHD). As expected, BMI was significantly lower ($P < 0.01$) in subjects with AN than in the control group. Subjects with AN had significantly lower BMD ($P < 0.01$) than the control group at all measurement sites (LS-BMD, FN-BMD, and TH-BMD), as measured by DXA and REMS. The mean duration of AN was 12.3 ± 11.3 years.

Moreover, seven women (16.3%) with AN had experienced at least one or more vertebral fractures.

REMS BMD Z-scores were consistent with DXA results at the lumbar spine and the entire femur. However, at the femoral neck, REMS BMD Z-scores were considerably lower ($P < 0.05$) than DXA results. Therefore, this study showed a good correlation between BMD obtained by DXA and REMS-estimated BMD at the lumbar spine ($r = 0.64$; $P < 0.01$), at the femoral neck ($r = 0.86$; $P < 0.01$), and at the total hip ($r = 0.84$; $P < 0.01$) in subjects with AN.

Osteogenesis Imperfecta

OI is a rare skeletal abnormality with a prevalence of 1 in 15,000 to 20,000. The hallmarks of OI are bone fragility, high frequency of fractures, bone deformities, and growth deficiency. Because the production of type 1 collagen in various tissues is impaired, individuals with OI may also have other clinical symptoms such as brittle teeth, blue sclerae, hearing loss, reduced respiratory function, and cardiac valvular regurgitation. The severity of OI varies from mild to extremely severe; the most severe form is perinatally lethal.[40]

OI is a hereditary disorder of connective tissue, mainly characterized by qualitative and quantitative alterations of bone collagen responsible for bone fragility and increased risk of fractures. Only the so-called classical mutations, found in one of the two genes (*COL1A1*/*COL1A2*) encoding for collagen type 1 alpha chains, were previously linked to OI. However, other mutations, or "non-classical mutations," were found recently.[41,42] They encode genes related to osteoblast development, bone mineralization, and the folding or posttranslational modification of collagen. Clinical heterogeneity and genetic heterogeneity are correlated.[43]

The most prevalent clinical characteristics of OI include blue sclera, dentinogenesis imperfecta, joint hyperlaxity, low stature, increasing bone abnormalities, hearing loss, and muscular weakness. Frequent fractures can also be caused by mild trauma or without any prior trauma. According to the Sillence classification, OI type I is the mildest clinical form and characterized by a mainly quantitative reduction in type 1 collagen; OI type III is the most severe nonlethal variant; type IV has a phenotype that falls somewhere between types I and III. OI type II is not found in adults because it is fatal during the prenatal period.

Again, there is a study in the literature evaluating REMS as a new approach to assessing bone health status in adults with OI.[44] This is an observational retrospective case-control study carried out in 2022. The study population consisted of 41 patients (21 males and 20 females) with clinical or genetic diagnoses of OI types I, III, or IV. For each patient with OI, a detailed clinical history was collected, especially focused on nonfractures (intrauterine fractures, time of the first fracture, fracture rate and location, etc.). The subjects were divided into groups based on their genetic diagnosis and illness phenotype. All OI patients were taking oral supplementation with calcium (500–1000 mg daily) and cholecalciferol (800 IU daily). Twenty-five patients (63%) were on neridronate treatment. The regimen called for the administration of neridronate (2 mg/kg, up to a maximum of 100 mg) every 3 months.

In all subjects, the following anthropometric variables were tested in standard conditions: weight, stature, and BMI. The BMI expresses the ratio of weight in kilograms divided by height in meters squared. In this study population, fasting venous blood samples were collected to measure serum levels of creatinine, alkaline phosphatase, calcium, and phosphate. They measured BMD with DXA and REMS in both patients with OI and controls. They measured the BMD at the level of the first four vertebrae of the lumbar spine (LS-BMD) and the level of the proximal femur considering the region of the femoral neck (FN-BMD) and the total hip (TH-BMD). All BMD scans were performed with DXA assessments following defined clinical practice protocols. Moreover, the diagnosis of osteoporosis and osteopenia was carried out based on the definition by the WHO and according to the International Society for Clinical Densitometry guidelines.[44]

Patients with OI had a mean age of 40.5 ± 18.7 years and therefore resembled the control group. As expected, weight and height were significantly lower in OI patients concerning the healthy control group ($P < 0.01$); on the contrary, 25OHD serum levels were significantly increased in OI subjects more than in controls. This is because all OI patients were taking vitamin D supplements. Patients with OI had significantly lower BMD ($P < 0.01$) than healthy control participants throughout all skeletal regions (TH-BMD, FN-BMD, and LS-BMD), as well as TBS. Moreover, 35 OI patients (85.4%) had experienced a fracture. A total of 22 OI patients had a history of vertebral fractures, and 10 OI patients reported hip fractures, whereas tibia or fibula fractures were present in 38 subjects. As expected, all patients with OI types I, III, and IV had a history of multiple fractures. Additionally, two OI patients experienced skull and femur fractures at delivery.

The findings of this study indicate that the longitudinal assessment of BMD and fracture risk using the REMS technology represents a new promising tool in patients with OI. Moreover, REMS technology, similar to TBS, can identify severe bone status impairment in patients with OI type I and OI types III and IV. More research is needed to confirm these preliminary findings, but more importantly, to develop additional metrics obtained from REMS analysis that better indicate bone quality.

Patients Receiving Peritoneal Dialysis

Chronic kidney disease (CKD) is associated with a wide range of bone mineral and endocrine disturbances known as mineral and bone disease (CKD-MBD), characterized by an increased risk of fragility fractures.[45] DXA is currently considered the gold standard for the measurement of BMD in clinical practice, and the Kidney Disease Improving Global Outcomes 2017 recommendations suggest BMD testing to assess for fracture risk in CKD patients.

In the literature is a study on patients undergoing peritoneal dialysis between June and September 2021.[46] They enrolled 41 patients in this study. Through interviews conducted during medical examinations and using electronic

medical records, information about the history of peritoneal dialysis, CKD, bone-related drugs, and fragility fractures was gathered for each patient. The diagnosis of CKD was made $\geq$ 3 months after kidney damage or a glomerular filtration rate < 60 mL/min/1.73 m^2 was observed, regardless of the cause. After an overnight fast, venous blood samples were taken in the morning. At the central laboratory, measurements of bone-specific alkaline phosphatase, calcium, and phosphorus were made using normal laboratory techniques.

The DXA and REMS scan was performed in all patients by a single expert operator who was blinded to the patient's clinical details. The DXA scanner was subjected to daily quality control and routine maintenance during the study period. The authors measured BMD at the anteroposterior lumbar spine (L1–L4) and femur (neck and entire hip), reported as T- and Z-scores. Additionally, the TBS was determined. Latero-lateral scans (LL) for BMD measurement were performed at the lumbar spine (L2–L3), with the acquisition of T-scores and Z-scores. Each patient had their BMD data from the DXA and REMS used to calculate two distinct fracture risk assessment tools: the FRAX and the FRAX-Derived Fracture Risk Assessment (DeFRA), an algorithm derived from FRAX and based on data on fracture risk in the Italian population.

The T-score of the AP DXA scan and both the LL DXA and REMS showed a statistically significant difference at the lumbar spine, whereas the LL DXA and REMS scan showed no difference. There was no discernible statistical difference between the femoral neck and whole-hip DXA and REMS T-scores. The TBS T-score was correlated with the T-score measured through DXA at all sites while not correlated with the REMS T-score at any site. In conclusion, this study demonstrates a promising agreement between DXA and REMS BMD values in a real-life PD context, as well as a subsequent fracture risk assessment.

Pregnancy

The mother's calcium metabolism and bone mineral state are particularly important during pregnancy. Throughout pregnancy, a significant amount of calcium must be transmitted from the mother to the fetus for the fetal skeleton to develop; 80% of this calcium must be delivered during the third trimester. To fulfill the increased calcium demands of the fetus, the mother's calcium metabolism changes in several ways.[47]

Although the higher levels of estrogens promote the formation of bone tissue, the fetal uptake of maternal calcium destined for skeletal development leads to maternal bone resorption. It is estimated that $\sim$ 200 to 300 mg of calcium every day is transferred across the placenta from the mother to the fetus. On this basis, the WHO recommends an extra dietary calcium intake of 200 mg/day for pregnant women compared with nonpregnant women.[48]

For these reasons, several studies in the literature have correlated the risk of osteoporosis in pregnant women. One study aimed to assess BMD in a group of healthy pregnant women. A nonconsecutive sample of 78 pregnant women with uncomplicated pregnancy at or $>$ 37 weeks of gestation were enrolled in this prospective case-control observational study. To measure the BMD of the femur, the study participants underwent a sonographic examination of the proximal femur using REMS technology. The pre-pregnant BMI, age, and ethnicity of a control group of nonpregnant women were matched to the BMD values obtained in the research group.[49]

The gestational age was calculated from crown-rump length measure between 11 (+ 0) and 13 (+ 6) weeks of gestation or head circumference if the first US scan was performed after 14 weeks. All pregnant women reported assuming regular folic acid and multivitamins since the early stages and the 16th week of pregnancy, respectively. Pregnant women's mean femoral BMD was found to be considerably lower than that of nonpregnant controls ($P = 0.0001$). Pregnant women's mean relative BMD loss was 8.1% when compared with the nonpregnant group as a reference.

Several studies have assessed changes in BMD during pregnancy at axial bones, like the femoral neck, using DXA, the gold standard for the evaluation of BMD in nonpregnant populations. Most of the research evaluated the mother's femoral BMD before conception and following delivery, but none were able to measure the actual decrease in BMD at the femoral neck during pregnancy due to the possible negative effects of radiation on the developing fetus. Some writers have suggested using quantitative US as a pregnant option for DXA. Another study aimed to assess longitudinally the changes in BMD at the femoral neck between the first and third trimester of pregnancy in a cohort of healthy participants using REMS technology.[50]

This was a single-center prospective cohort study that included healthy participants with an uncomplicated singleton pregnancy before 14 completed weeks of gestation. Since the early stages of pregnancy, all individuals reported taking multivitamins or folic acid daily. When the first-trimester screening for chromosomal abnormalities was conducted, participants were approached between 11 + and 13 + 6 weeks of gestation. If the screening revealed a low risk of significant trisomies (21, 18, and 13), they were enrolled.

To determine the BMD using REMS technology, a sonographic examination of the femoral neck was performed on each of the enrolled participants. After the first-trimester US screening (11–13 weeks of gestation), a single obstetrician with $>$ 5 years of expertise in the field conducted a sonographic assessment of the mother's femoral neck. This procedure was repeated for the usual antenatal evaluation (37–39 weeks of pregnancy). Additionally, if any of the following conditions materialized between the two US examinations, participants were likewise eliminated from the study group: pregnancy complications (e.g., hypertensive disorders, gestational diabetes, cholestasis, gestational hypothyroidism), intrauterine fetal death, spontaneous or indicated preterm birth, postnatal diagnosis of congenital anomalies, and the need for medications that may interfere with bone metabolism, such as heparin, corticosteroids, or vitamin D intake $>$ 400 IU/day.

Over 7 months, 189 people were identified as eligible for the study, enrolled, and had their BMD measured at the

femoral neck during the first trimester. During the period between the first- and third-trimester examination, some participants experienced complications, others preterm delivery or even abortion. From the first to the third trimester of pregnancy, there was a significant reduction in BMD at the femoral neck ($P < 0.001$). A total of 63 participants experienced a reduction of the BMD throughout the pregnancy, with a maximal reduction of 5.5%. In contrast, two subjects' femoral neck BMD increased by 0.2% and 0.8% between the first and third trimesters of pregnancy, respectively.

Conclusion

REMS is an innovative fast and radiation-free technology for evaluating and monitoring bone health status, both at quantitative and qualitative levels. Thanks to its radiation-free approach, REMS can be applied to all populations (e.g., young, pregnant, fragile, bedridden patients). REMS is suitable for early diagnosis in clinical practice, short-term follow-up, mass population surveys, and prevention programs.

In summary, REMS technology has shown value in the diagnosis of osteoporosis and the prediction of fracture risk in sizable populations. This technology has several benefits, such as (1) the ability to assess bone quality; (2) the ability to get around some of the drawbacks of DXA; (3) the potential to enable clinicians to assess bone status with periodic follow-up without radiation in situations where other radiologic methods (such as childhood or pregnancy) are not useful; and (4) the portability, user friendliness, and long-term viability of REMS. However, currently noninvasive procedures are unavailable for assessing bone quality in clinical practice. This lack has stimulated interest in other techniques able to estimate bone status and the risk of fragility fracture.[51]

In the last 20 years, QUS, which measures bone features by US wave attenuation and reflection, has been regarded as an intriguing technology due to its low cost, lack of ionizing radiation, and portability. For these qualities, QUS may provide some advantages over the DXA approach. Future studies and continuing research will help us better understand the function of REMS in the diagnosis of patients with osteoporosis and follow-up with DXA.

Conflict of Interest
None declared.

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