Radiofrequency echographic multispectrometry (REMS) in rare bone conditions

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ABSTRACT

In recent years there has been a growing interest in radiofrequency echographic multispectrometry (REMS), an innovative technology, free of ionized radiation, that is capable of providing important information on bone status. In particular, REMS has been shown to measure bone mineral density (BMD) at axial skeletal bones with a precision, repeatability and accuracy not inferior to those of dual-energy X-ray absorptiometry (DXA). Moreover, REMS may be useful in the assessment of impaired bone quality (e.g., in patients with type 2 diabetes mellitus) and to predict fragility fracture risk. Due to these characteristics, REMS could be usefully used in the diagnosis and follow up of rare bone diseases. In 41 adult subjects (mean age 40.5 ± 18.7 years) with osteogenesis imperfecta (OI), BMD values at all skeletal sites, obtained using both DXA and REMS, were significantly lower than in controls. BMD by REMS values were significantly lower in patients with types III and IV versus type I OI, whereas BMD by DXA did not differ significantly between the two groups. REMS has also demonstrated excellent diagnostic accuracy in some patients suffering from McCune-Albright or Ehlers-Danlos syndromes. Furthermore, with REMS it is to obtain the real BMD value in the presence of artifacts, and, being free of ionizing radiation, it could be particularly advantageous in children and in women of childbearing age or during pregnancy and breastfeeding. In conclusion, on the basis of these preliminary data, REMS can be considered a precise and reliable technique for the evaluation and monitoring of bone status in individuals with rare bone diseases.

KEYWORDS

Rare bone diseases, bone mineral density (BMD), dual-energy X-ray absorptiometry (DXA), radiofrequency echographic multispectrometry (REMS), osteogenesis imperfecta.

Introduction

Rare diseases, by definition, have a prevalence lower than a certain threshold, which for the European Union is set at 5 cases per 10,000 individuals. It is important to underline that although each rare disease affects a relatively small number of people, there are many people affected by rare diseases overall. Among these diseases, rare disorders affecting the skeletal system are particularly complex. They arise from anomalies in the intricate processes of bone development, from growth to the maintenance of skeletal balance, and remain very difficult to clinically diagnose and treat, due to their considerable number and variability. So far, more than 300 different forms of rare skeletal disease have been classified and the treatment of these conditions is a significant burden for healthcare systems [1]. Early diagnosis and close follow-up of these diseases are fundamentally important, to reduce complications and the resulting economic and social costs. Dual-energy X-ray absorptiometry (DXA) is a technique used to measure bone mineral density (BMD) and it is universally recognized as the gold standard for the diagnosis of osteoporosis [2]. However, DXA also has some important limitations as it uses ionizing radiation which limits its use in pediatrics and in women of childbearing age. Furthermore, DXA overestimates bone mineral content in the presence of artifacts such as aortic calcifications, vertebroplasties, vertebral fractures, and structural abnormalities caused by osteoarthritis [3]. High-resolution peripheral quantitative computed tomography and magnetic resonance imaging rare important tools for quantitative, qualitative, and structural evaluation of trabecular and cortical bone. However, due to higher exposure to ionizing radiation and the costs involved, they cannot be used in clinical practice [4]. For this reason, there is growing interest in new non-invasive techniques that can be used to assess bone status from both a quantitative and qualitative point of view. Among these, a more recent and attractive tool is radiofrequency echographic multispectrometry (REMS).

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REMS

Fundamentally, REMS is designed to assess native raw unfiltered radiofrequency (RF) ultrasound signals, obtained while performing an echographic examination of the proximal femur and lumbar vertebrae [5]. Since these signals are normally filtered during the conventional B-mode image rebuilding pro-

cess, REMS makes it possible to capture more information on the features of the bone tissues being evaluated.[5] Bone status is assessed by comparing the analyzed signal spectra with previously derived reference spectral models for the pathological and normal conditions being considered. Actually, the spectral modifications induced by the physical properties of the bone structure, which has backscattered the ultrasound signals. This results in a BMD estimation, and the consequent diagnostic classification of the bone as healthy, osteopenic, or osteoporotic (Fig.1).

Some papers have reported that REMS offers good precision and a diagnostic accuracy similar to that of DXA [6]. Recent studies have demonstrated the ability of REMS to diagnose osteoporosis; in particular, in a follow-up period of 5 years, REMS showed a higher sensitivity than DXA in the detection of female subjects prone to fragility fractures [6,7]. Furthermore, lower BMD values at the lumbar spine, obtained by REMS, were significantly associated with a history of major fragility fractures in the type 2 diabetes mellitus (T2DM) population, whereas BMD values measured by DXA were not. This suggests that REMS may be useful in the assessment of impaired bone quality in patients with T2DM [8]. Recently, an additional REMS-based parameter, the fragility score (FS), has been introduced [9]. The FS is independent of BMD and it is obtained by comparing patient-specific spectral profiles with population-based anthropometrically-matched models of "fractured" and "non-fractured" subjects [9]. Furthermore, a prospective study involving 1989 patients recently demonstrated that the FS is more capable of predicting fracture risk in both female and male subjects than BMD T-score values obtained by means of either DXA or REMS [10]. The possibility of evaluating bone status using REMS in young women is revolutionary because the technology can be used safely during the fertile years, as well as during pregnancy and breastfeeding. This is particularly interesting for women of childbearing age with rare bone diseases and for those with pregnancy- and lactation-associated osteoporosis (PLO), a rare form of osteoporosis that appears during the third trimester of pregnancy or breastfeeding [4,11,12]. Another advantage of REMS highlighted in the literature is that the technique may be able to overcome the problem of common artifacts, such as osteoarthritis, vascular calcifications, and vertebroplasty of the lumbar spine, which affect the BMD values obtained by DXA [12].

Due to these characteristics, REMS could be usefully used in the diagnosis and follow up of rare bone diseases.

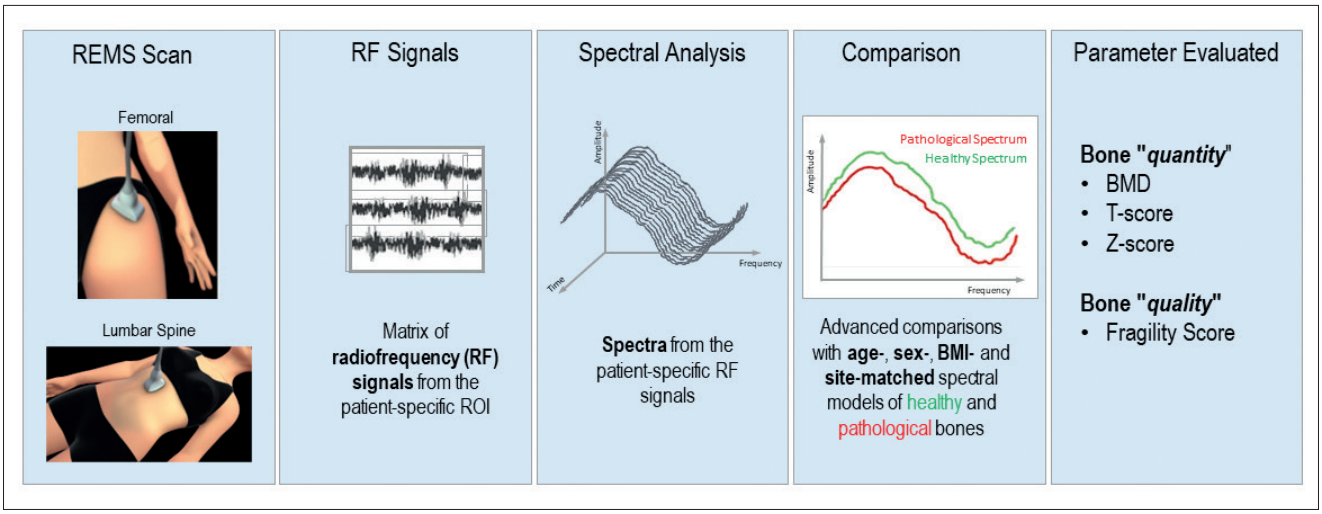
REMS in osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a rare (affecting one in 15-20,000 individuals) hereditary disease of the connective tissue, characterized mainly by qualitative and quantitative alterations of bone collagen leading to bone fragility and an increased risk of fractures. Patients with OI have a very high risk of suffering fragility fractures, especially during childhood and adolescence [13,14]. According to the Sillence classification, based on clinical severity and radiographic criteria, OI type I, characterized by a mainly quantitative reduction in type I collagen, is the mildest clinical form; OI type III is the most severe non-lethal form, while OI type IV has an intermediate phenotype between types I and III. OI type II is not found in adults, because it is lethal in the perinatal period [14]. Many studies have reported that bone microarchitecture is markedly altered in OI. In fact, trabecular thickness and volumetric bone mass are lower, and cortical thickness is also reduced with increased intracortical porosity [15]. All these changes in bone structure alter the bone biomechanics and increase bone fragility in individuals with OI [15].

In 41 adults (mean age 40.5 ± 18.7 years) with OI and in a group of healthy controls, BMD at various skeletal sites was assessed with both the DXA technique and the REMS technique. Moreover, the trabecular bone score (TBS) was calculated from the standard antero-posterior DXA scan of the lumbar spine. The patients were divided into groups according to type of OI: type I (n = 32, 78.0%), type III (n = 5; 12.2%), and type IV (n = 4; 9.8%). Almost all the patients with OI had a history of several fragility fractures located mainly at the radius, tibia, vertebrae, and femur [16].

BMD values, obtained using both DXA and REMS, were significantly lower in patients with OI compared with controls at all skeletal sites. Figure 2 shows the BMD values at the lum-

Figure 1 Radiofrequency echographic multispectrometry (REMS).

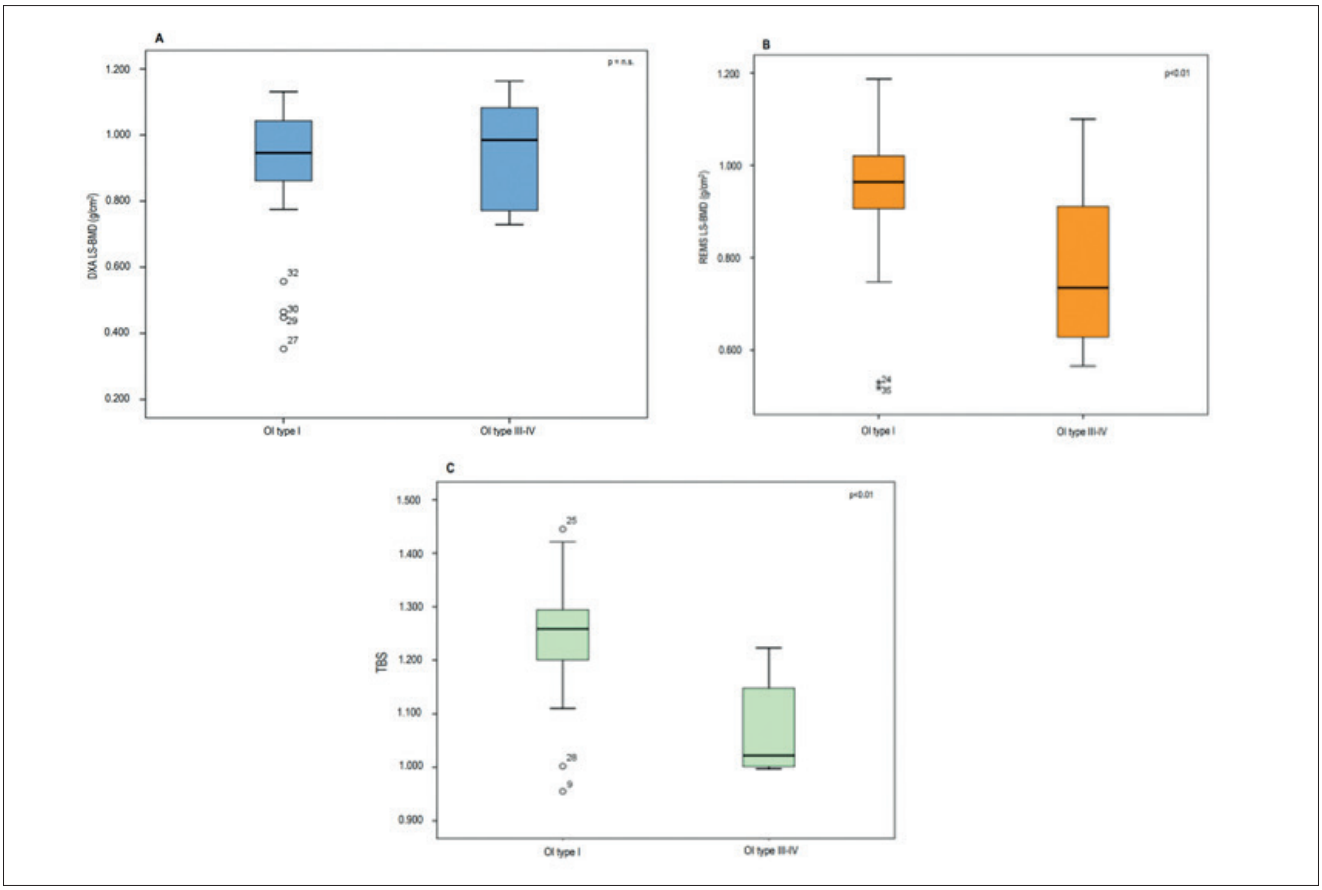


bar spine (obtained using both techniques), and the TBS values of patients with type I OI, and of those with types III and IV OI. BMD values measured by DXA were not significantly different between the two groups. On the contrary, both BMD by REMS and TBS values were significantly lower in patients with type III and IV OI compared with the type I cases (Fig.2). Furthermore, the TBS showed a highly significant correlation with BMD at the lumbar spine measured by REMS (p>0.001), but an only marginally significant one (p=0.05) with lumbar spine BMD measured by DXA [16]. The data obtained in these patients allow us to draw two important considerations. First of all, they confirm that patients' bone status can be evaluated using REMS, a technique that does not use ionizing radiation. This finding is important, because OI patients, given their high risk of fractures, require repeated radiological examinations. Furthermore, the use of a technique free of ionizing radiation, such as REMS, could be particularly advantageous during adolescence and in women of childbearing age or during pregnancy and breastfeeding [11,16]. Another consideration is that BMD assessment with REMS could overcome the limitations of BMD measurement by DXA in patients with OI. The literature data indicate that BMD measured by DXA is only slightly reduced and sometimes even increased in many patients with OI; moreover, only a small percentage of patients display osteoporotic T-scores, and fragility fractures in OI patients cannot be fully explained by low BMD [17] In fact, OI is characterized by reduced bone quality due to the presence of defects in the bone matrix and mineralization which are in addition to the alterations of bone microarchitecture [15]. Moreover, REMS technology, similarly to the TBS, can identify severe bone status impairment between patients with moderate to severe OI-III–IV and those with the mildest OI-I [18]. Furthermore, the presence of scoliosis and vertebral fractures, particularly frequent in subjects with types III and IV OI, determine a marked overestimation in the evaluation of vertebral BMD by DXA, while not significantly influencing TBS and BMD by REMS values.

REMS in other rare bone diseases

McCune-Albright syndrome (MAS) is a rare sporadic disease due to somatic gain-of-function mutations of the *GNAS* gene. It has an estimated prevalence of between 1/100,000 and 1/1,000,000. The cardinal clinical manifestations of the syndrome include the classic triad of monostotic/polyostotic fibrous dysplasia, café au lait skin pigmentation, and several hyperfunctioning endocrinopathies, such as gonadotropin-independent precocious puberty, growth hormone (GH) excess, non-autoimmune hyperthyroidism, hyperprolactinemia, and neonatal hypercortisolism [19,20]. Pain is very frequent and can significantly impair mobility and quality of life. Figure 3 illustrates the clinical case of a 52-year-old woman suffering from MAS. This patient presented polyostotic fibrous dysplasia evident on radiographic and scintigraphic examination

Figure 2 Lumbar spine BMD by DXA and by REMS and TBS values in type I and type III/IV OI patients.



which affected: the maxillary sinuses, left hemimandible, right hemipelvis, right and left femur, and distal diaphysis of the left tibia. The patient was being treated with bisphosphonates and was periodically monitored for BMD. Assessment of BMD by DXA showed very high T-score values at the level of the lumbar spine and femurs (e.g., at the left femur Neck: 3.9 and Total Hip: 4.2). The BMD by REMS assessment instead showed markedly lower T-score values (-1.3 and -0.8, for Neck and Total Hip, respectively), highlighting a better characterization of the bone structure using the REMS technique (Fig.3). This clinical case suggests the usefulness of REMS in the therapeutic monitoring of individuals with MAS, a rare disease characterized in adulthood by an increased risk of fracture [20,21].

Ehlers-Danlos syndromes

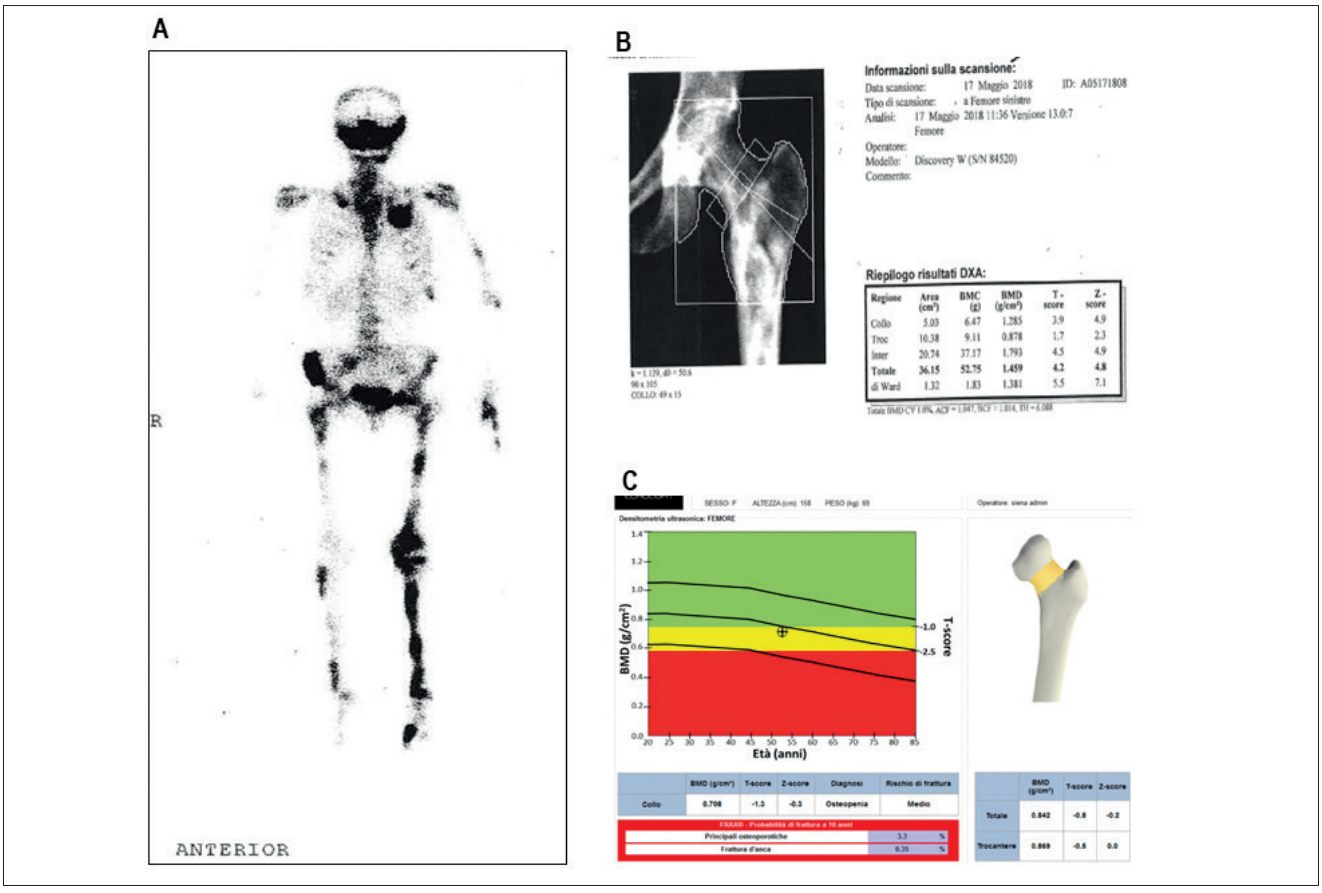
Ehlers-Danlos syndromes (EDS) are a clinically and genetically heterogeneous group of hereditary connective tissue disorders with maximum expression in the soft tissues and, in particular, skin, joints and cardiovascular system. Skin hyperelasticity, joint hypermobility and fragility of vessels and internal organs are the clinical triad most representative of these syndromes [22]. The most common forms of EDS are due to alterations in the genes that code for collagen types III and V. Bone involvement in this syndrome has long been debated. Some more recent studies have found that EDS patients present reduced BMD values and an increased risk of fragility fractures, and recent studies have reported a high prevalence of radiological vertebral fractures in adults with EDS, even in the presence of normal BMD as assessed by DXA. Moreover, the presence and severity of vertebral fractures were significantly associated with back pain [23]. The mechanisms leading to skeletal fragility in EDS may be similar to those occurring in OI, a disease due to a primitive defect in type I collagen synthesis. Moreover, EDS patients have a cortical bone size deficit compared with controls, which may be due to reduced muscle cross-sectional area [24].

Figure 4 illustrates the clinical case of a 61-year-old woman suffering from an EDS. A DXA assessment showed marked osteoporosis (T-score Neck: -3.4, T-score L1-L4: -4.8), and she was also found to have equally low TBS values (L1-L4: 1.204; T-score: -2.9). Bone densitometry with REMS technology also highlighted osteoporosis (T-score Neck: -3.5, T-score L1-L4: -4.1). The results obtained in this patient show that the REMS method assesses bone status as correctly and reliably as DXA and TBS do.

Acromegaly

Acromegaly is a rare disease characterized by elevated levels of GH and insulin-like growth factor I (IGF-I), primarily due to a pituitary adenoma. The condition may cause skeletal alterations and fragility fractures. In fact, the excess of GH and IGF-I promotes the development of cortical thickness, but at the same time stimulates cortical porosity, consequently increasing the risk of fractures, especially at the vertebral level. In a study

Figure 3 Femoral BMD by DXA and by REMS in a McCune-Albright syndrome patient.



conducted by Polish endocrinologists in 33 patients with acromegaly (25 women and 8 men), BMD values at all skeletal sites measured with REMS did not differ significantly from those measured with DXA [25].

Conclusions

In rare bone diseases, REMS allows accurate and reliable assessment of bone health comparable to DXA and TBS. Furthermore, the possibility of using ultrasound technology without ionizing radiation could make REMS an important technology for evaluating and monitoring patients suffering from rare bone diseases. With REMS, it is also possible to obtain the real BMD value in the presence of artifacts and to identify patients with the most severe disease forms, who are at greater risk of fracture. Moreover, in women of childbearing age affected by rare bone diseases, REMS allows bone health to be monitored accurately and safely during pregnancy and breastfeeding [12]. Finally, rare bone diseases, characterized by peculiar structural and bone matrix alterations, represent fascinating experimental models for studying and developing the potential of REMS technology to provide information on the qualitative characteristics of bone tissue.

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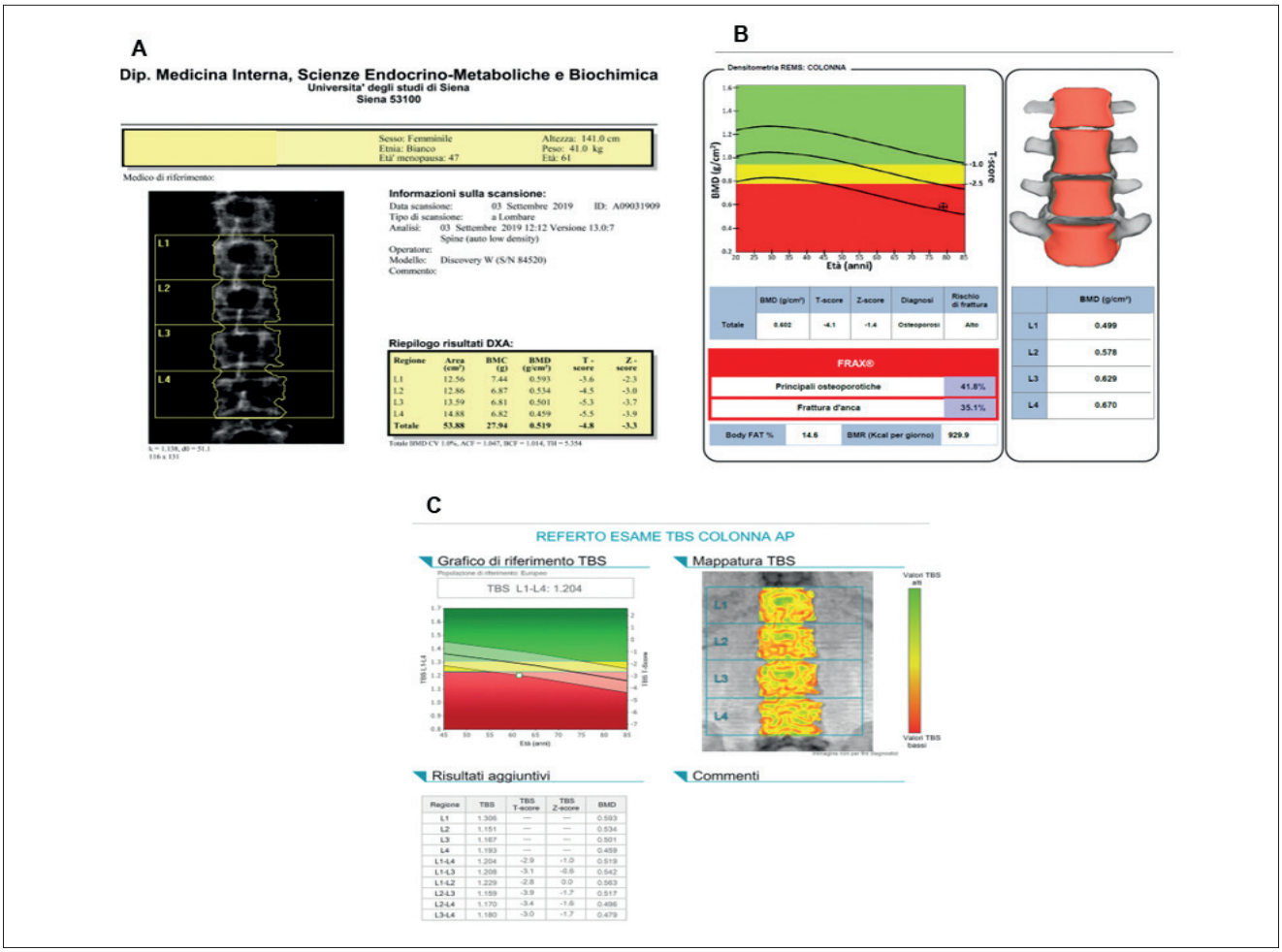
Figure 4 Lumbar BMD by DXA (A) and by REMS (B) and TBS (C) in an Ehlers-Danlos patient.



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