CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

GENERAL MEDICINE

REMS (RADIOFREQUENCY ECHOGRAPHIC MULTI-SPECTROMETRY) TECHNOLOGY FOR THE EVALUATION OF BONE DENSITY IN PATIENTS WITH SPONDYLOARTHRITIS

DOCTORAL THESIS ABSTRACT

Doctoral supervisor

PROF. UNIV. DR. ARAMĂ ȘTEFAN SORIN

PhD Student:

BADEA IONUȚ-ANDREI

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1. INTRODUCTION

Considering the polymorphism of inflammatory rheumatic diseases and their potential complications that can negatively impact the patients' quality of life, combined with the financial burden of osteoporosis—especially fragility fractures—on national health systems, it is necessary to implement reliable and rapid diagnostic methods. Radiofrequency Echographic Multi-Spectrometry (REMS) is a technique recently introduced into clinical practice across various pathologies, aiming to identify patients at risk for bone fragility. However, in rheumatology, REMS has not yet been deeply explored, which constitutes the foundation of this thesis.

Osteoporosis associated with rheumatoid arthritis (RA) is of particular interest, given the significant evidence supporting bone involvement in RA. RA is currently considered a major risk factor for bone demineralization and secondary fragility.

Importantly, RA is not the only rheumatic pathology that frequently presents this increased bone fragility. Osteoporosis is observed even in early forms of axial spondyloarthritis (axSpA), including both radiographic and non-radiographic forms.

The diagnostic niche of REMS could intuitively cover the radiographic forms of axSpA (r-axSpA), since osteosclerotic structural lesions may falsely elevate bone mineral density (BMD) values obtained through DXA. Advanced methods such as quantitative computed tomography (QCT) or special magnetic resonance imaging (MRI) can measure BMD with high precision, but their application in routine clinical settings is limited by radiation exposure, long scan times, and significant costs.

At first glance, REMS appears to be the most advantageous option for evaluating bone density and fragility in such cases. Although this thesis mainly addresses a small group of inflammatory rheumatic pathologies, the applicability of REMS is broader. For instance, its radiation-free profile opens opportunities for safe densitometric evaluation in pregnant women — a population often affected by systemic rheumatic diseases such as systemic lupus erythematosus (SLE).

Thus, this research was designed to include a significant number of relevant patients from various age groups. The first phase of the study assesses general bone health among young adults in Romania, correlating mineralization changes with diet, smoking, comorbidities, and physical activity. Subsequently, we evaluate the equivalency of BMD results obtained by DXA and REMS in a population without rheumatic inflammation. Finally, REMS assessments in the general population are compared with those in patients with SpA to determine factors influencing bone density and quality, aiming for a comprehensive characterization of both REMS as a method and bone mineralization disorders associated with SpA.

2. OBJECTIVES

The investigation of the applicability of REMS in different scientific and clinical situations to characterize the precision of BMD and FS values obtained through this method.

The objective of the first study was to identify bone quality in a group of young adults in Romania and to describe the potential impact of risk factors on bone mineralization.

The main factors considered were:

- Diet;
- Body Mass Index (BMI);
- Physical activity and its type;
- Tuxedo status;
- Alcohol consumption;
- Presence of hormonal disorders;
- Comorbidities and specific medications.

The primary objective of the second study was the identification and description of differences between BMD, T-scores of the lumbar spine and femoral neck, and the diagnostic rate of osteopenia and osteoporosis. Secondarily, we attempted to identify and describe the impact of risk factors for bone mineralization deficits in the studied cohort.

The third study aimed to compare, identify, and characterize the differences between DXA and REMS examinations at the lumbar spine in patients diagnosed with axial spondyloarthritis (axSpA). A secondary goal was to identify the subgroup of patients who would benefit the most, both diagnostically and prognostically, from lumbar REMS evaluation.

Additionally, we pursued the identification of the utility of the Fragility Score (FS) in monitoring the group of axSpA patients described above, specifically concerning vitamin D supplementation. Secondary objectives included describing the utility of supplementation in terms of muscular strength and fall risk in this group.

Subsequently, we chose to present the case of two patients (brothers) who presented at the Department of Internal Medicine and Rheumatology of the "Dr. I. Cantacuzino" Clinical Hospital in Bucharest, where REMS examination allowed for correct and tailored medical decisions adapted to their forms of spondyloarthritic involvement.
We will delve into details about one case that seemed more interesting and suggestive for the purposes of this work, offering perspectives on lesser-used therapeutic approaches.

In the final investigation, the objective was to describe the influence of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic DMARDs (csDMARDs), and biological DMARDs (bDMARDs) on bone mineralization and fragility in patients with axSpA and psoriatic arthritis (PsA).

Secondarily, we aimed to describe the evolution of these patients according to the degree of disease activity, by identifying the influence of disease duration and biological inflammatory syndrome, defined by pathological increases in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

3. MATERIALS AND METHODS

Several studies were designed to evaluate REMS in different clinical situations to allow for the most complete description of the method.

The recruitment of subjects for all studies was carried out within the "Dr. I. Cantacuzino" Clinical Hospital in Bucharest, as well as within two private clinics in Bucharest.REMS analysis was performed for all studied groups, aiming to obtain information related to bone mineral density (BMD) and calculation of the T-score.Where and when possible, we also added fragility score (FS) data to the analysis.

Verbal and written approvals were obtained from the ethics committee of the "Dr. I. Cantacuzino" Clinical Hospital and from the two private clinics for the recruitment and analysis of subjects.

All enrolled individuals signed an informed consent regarding the anonymous processing of data, and agreement was obtained for performing the REMS investigation after explaining the procedure.

In some studies, inclusion and exclusion criteria were applied to better select the investigated population and to reduce the risk of bias as much as possible. These were applied to patients with spondyloarthritis and consisted of:

- A confirmed diagnosis of axial spondyloarthritis based on ASAS classification criteria;
- Completion of routine analyses according to regular hospital or clinic visits, including inflammatory markers (C-reactive protein and erythrocyte sedimentation rate);
- Proof of HLA-B27 testing at any time in the patient's history, documented through the patient's medical records;
- Absence of comorbidities that could influence bone metabolism (for example, diabetes mellitus, hyperparathyroidism, hypothyroidism);

- Absence of therapies that influence bone metabolism (glucocorticoids under any administration form);
- Understanding and signing of informed consent;
- Recent measurement (within one month) of 25-OH-Vitamin D levels or carrying out such measurement within one month based on the medical recommendation during the routine medical visit;
- Agreement to comply with reevaluations established within the study protocol.

Furthermore, in the final and most laborious study, 70 patients diagnosed with axial spondyloarthritis and psoriatic arthritis based on the ASAS and CASPAR classification criteria were enrolled. The enrollment period extended from January 2020 to January 2022, with initial evaluations and reevaluations after one year. Recruitment was performed within a public hospital and a private clinic, and densitometric evaluation was performed in a third private clinic. Patients were informed about the purpose of the study and the procedures involved and signed an informed consent.

Blood analyses were performed during routine hospital visits or based on referrals, without patients incurring additional costs. Additionally, densitometric evaluation was conducted by means of Radiofrequency Echographic Multi-Spectrometry (REMS), obtaining values of bone mineral density (BMD), T-score, and fragility score (FS).

The obtained data from all studies were initially stored in Microsoft Excel, where a primary analysis was conducted prior to performing statistical testing. Statistical processing was performed using MiniTab v.20 (MiniTab LLC) and online through DataTab (datatab.net), with graphs and tables included in the analysis resulting from this online processing.

4. WHAT IS THE BONE QUALITY OF YOUNG ADULTS IN ROMANIA?

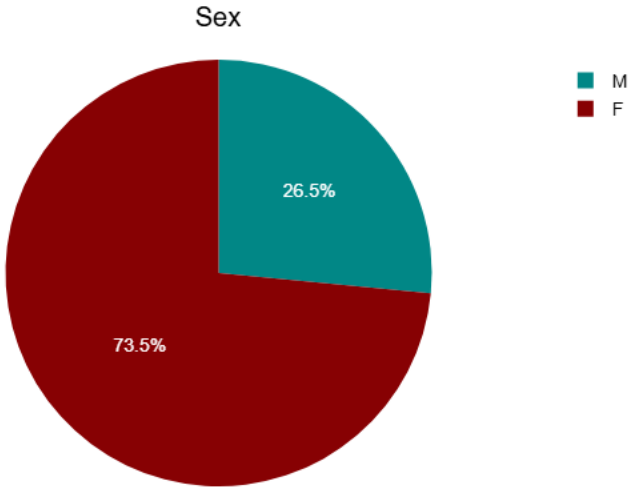

Figure 1 – Distribution by sex of the studied group.

*Table 1 – **Descriptive statistics of the studied group** ([a]Chi2, p=0.529; [b]t-test, p=0.009; CT-test, p<0.005; dt-test, p=0.068; [e]t-test, p=0.047; [f]t-test, p=0.033)*		
Parameter	**Men (n=13)**	**Women (n=36)**
Protein-lipid diet[a]	7 (14.29%)	25 (51.02%)
Balanced diet[a]	4 (8.16%)	5 (10.2%)
Diet rich in carbohydrates[a]	2 (4.08%)	5 (10.2%)
Diet rich in fish[a]	0 (0%)	1 (2.04%)
Ageb	23.31 ± 1.44	22.14 ± 1.29
Weightc	64.15 ± 19.56	61.28 ± 11.27
Heightc	170.69 ± 9.43	170.14 ± 7.63
BMId	22.9 ± 4.47	20.78 ± 3.11
Lumbar spine BMD (g/cm²)[e]	1.28 ± 0.14	1.12 ± 0.26
Femoral neck BMD (g/cm²)[f]	0.97 ± 0.13	0.81 ± 0.26
Lumbar spine Z-score[c]	1.8 ± 1.26	0.61 ± 1.06
Femoral neck Z-score[c]	0.45 ± 0.88	-0.73 ± 0.59

Regarding physical activity, it was classified according to the type of activity:

- **Cardio** – greater focus on regulating heart rate during physical effort, with long-duration physical activity;

- **Endurance** – stimulation of high-intensity physical activity alternating with rest periods, such as high-intensity interval training (HIIT);
- **Strength** – focused on increasing muscle mass, involving exercises with barbells, dumbbells, etc.;
- **Yoga/Pilates/Tai-chi** – exercises that focus on maintaining joint mobility, without significant increase of heart rate during effort.

Among the identified comorbidities we find:

- **Asthma** – 1 case, without treatment;
- **Beta-thalassemia minor and vitiligo** – 1 case, without treatment;
- **Autoimmune thyroiditis** – 2 cases, of which one is associated with hypothyroidism under treatment with Levothyroxine 50 μg/day;
- **Insomnia** – 1 case, under treatment with Agomelatine 25 mg/day;
- **Renal lithiasis** – 1 case, without treatment;
- **Polycystic ovary syndrome and chronic pyelonephritis** – 1 case, under treatment with Metronidazole 500 mg/day;
- **Mitral valve prolapse** – 1 case, under treatment with Bisoprolol 2.5 mg/day;
- **Ulcerative hemorrhagic colitis** – 1 case, under treatment with Mesalazine 1 g/day;
- **Gilbert's syndrome** – 1 case, without treatment.

No chronic alcohol consumption was identified in the studied group; the smoker to non-smoker ratio was approximately 1:3.

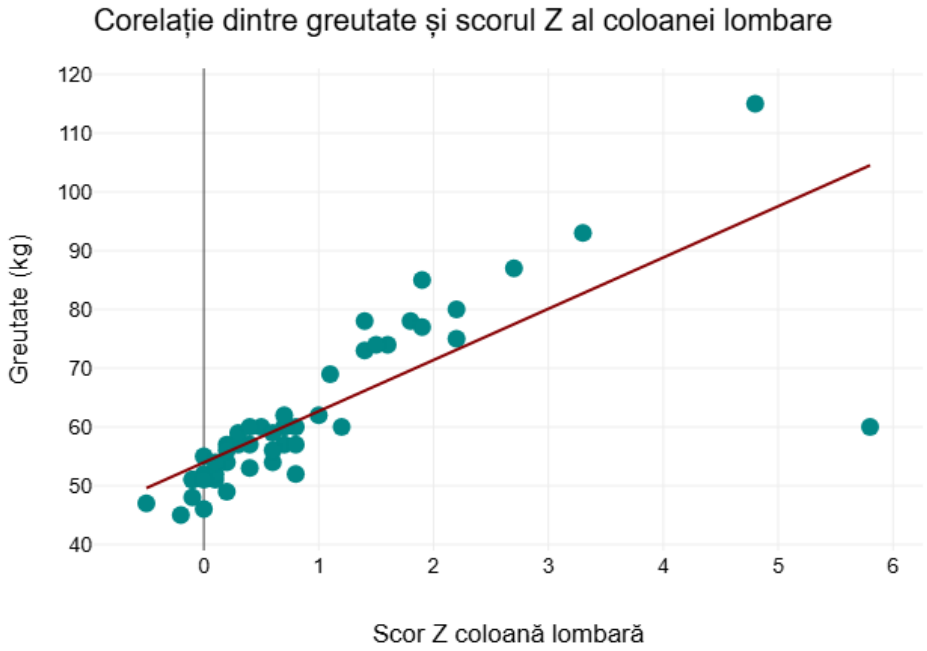

Figure 2 – Spearman's correlation with r=0.9 and p<0.001 between weight and lumbar spine Z score.

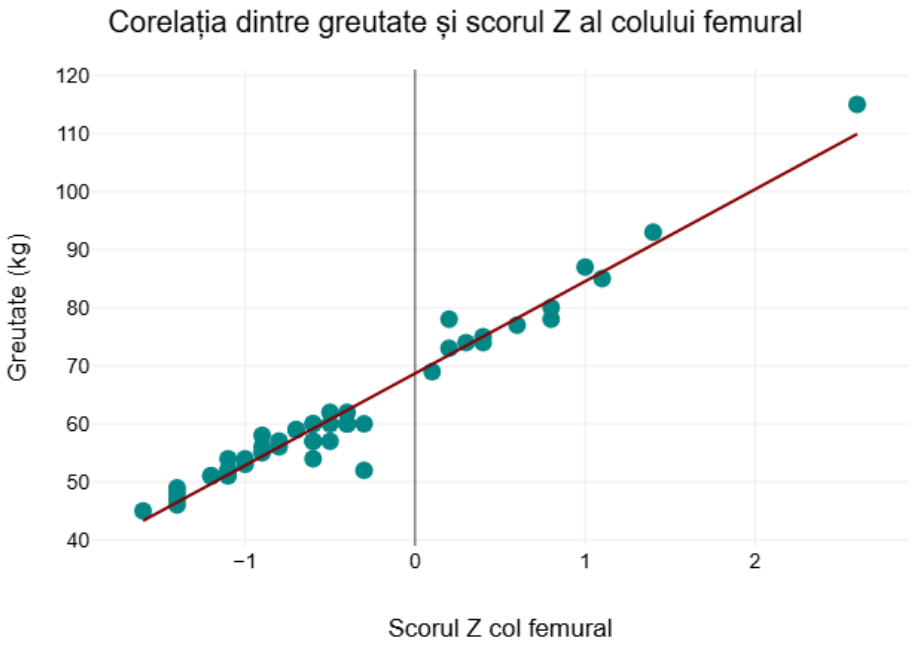

Figure 3 – Correlation between weight and femoral neck Z score measured by REMS. The Sperman test proves a high, positive correlation with r=0.94 and p<0.001.

Table 2 – Descriptive statistics of the studied lot.

		n	Frequency %	Average	Standard deviation	Minimum	Maximum	Average ± Std.
	Overweight	56	10.51%	0.73	0.11	0.55	0.94	0.73 ± 0.11
	Normal weight	32	6%	0.72	0.11	0.57	0.92	0.72 ± 0.11
	Grade I obesity	10	1.88%	0.78	0.14	0.55	0.95	0.78 ± 0.14
	Underweight	1	0.19%	0.53	Nan	0.53	0.53	0.53 ± NaN
	Overweight	301	56.47%	0.69	0.09	0.5	0.94	0.69 ± 0.09
	Normal weight	111	20.83%	0.66	0.11	0.5	0.94	0.66 ± 0.11
	Grade I obesity	16	3%	0.76	0.08	0.57	0.86	0.76 ± 0.08
	Underweight	6	1.13%	0.71	0.15	0.58	0.91	0.71 ± 0.15
	Overweight	56	10.51%	0.76	0.1	0.56	0.94	0.76 ± 0.1
	Normal weight	32	6%	0.76	0.13	0.55	0.94	0.76 ± 0.13
	Grade I obesity	10	1.88%	0.79	0.11	0.62	0.93	0.79 ± 0.11
	Underweight	1	0.19%	0.68	Nan	0.68	0.68	0.68 ± NaN
	Overweight	301	56.47%	0.74	0.11	0.55	0.95	0.74 ± 0.11
	Normal weight	111	20.83%	0.76	0.11	0.57	0.95	0.76 ± 0.11
	Grade I obesity	16	3%	0.76	0.08	0.57	0.94	0.76 ± 0.08
	Underweight	6	1.13%	0.72	0.14	0.57	0.92	0.72 ± 0.14
	Overweight	56	10.51%	0.79	0.12	0.56	0.96	0.79 ± 0.12
	Normal weight	32	6%	0.78	0.14	0.55	0.96	0.78 ± 0.14

Grade I obesity	10	1.88%	0.82	0.12	0.62	0.95	0.82 ± 0.12
Underweight	1	0.19%	0.71	Nan	0.71	0.71	0.71 ± NaN
Overweight	301	56.47%	0.77	0.12	0.55	0.97	0.77 ± 0.12
Normal weight	111	20.83%	0.78	0.12	0.56	0.97	0.78 ± 0.12
Grade I obesity	16	3%	0.77	0.11	0.57	0.96	0.77 ± 0.11
Underweight	6	1.13%	0.75	0.16	0.57	0.95	0.75 ± 0.16
Overweight	56	10.51%	0.72	0.15	0.5	0.94	0.72 ± 0.15
Normal weight	32	6%	0.73	0.13	0.52	0.92	0.73 ± 0.13
Grade I obesity	10	1.88%	0.77	0.15	0.55	0.95	0.77 ± 0.15
Underweight	1	0.19%	0.79	Nan	0.79	0.79	0.79 ± NaN
Overweight	301	56.47%	0.71	0.13	0.5	0.95	0.71 ± 0.13
Normal weight	111	20.83%	0.71	0.13	0.5	0.94	0.71 ± 0.13
Grade I obesity	16	3%	0.68	0.11	0.51	0.86	0.68 ± 0.11
Underweight	6	1.13%	0.69	0.16	0.54	0.91	0.69 ± 0.16
Overweight	56	10.51%	47.41	16.26	20	79	47.41 ± 16.26
Normal weight	32	6%	34.78	11.49	20	64	34.78 ± 11.49
Grade I obesity	10	1.88%	35.8	4.32	31	45	35.8 ± 4.32
Underweight	1	0.19%	74	Nan	74	74	74 ± NaN
Overweight	301	56.47%	62.19	13.64	20	89	62.19 ± 13.64
Normal weight	111	20.83%	51.25	15.95	22	91	51.25 ± 15.95
Grade I obesity	16	3%	48.75	16.99	25	76	48.75 ± 16.99
Underweight	6	1.13%	36.17	12.35	27	54	36.17 ± 12.35

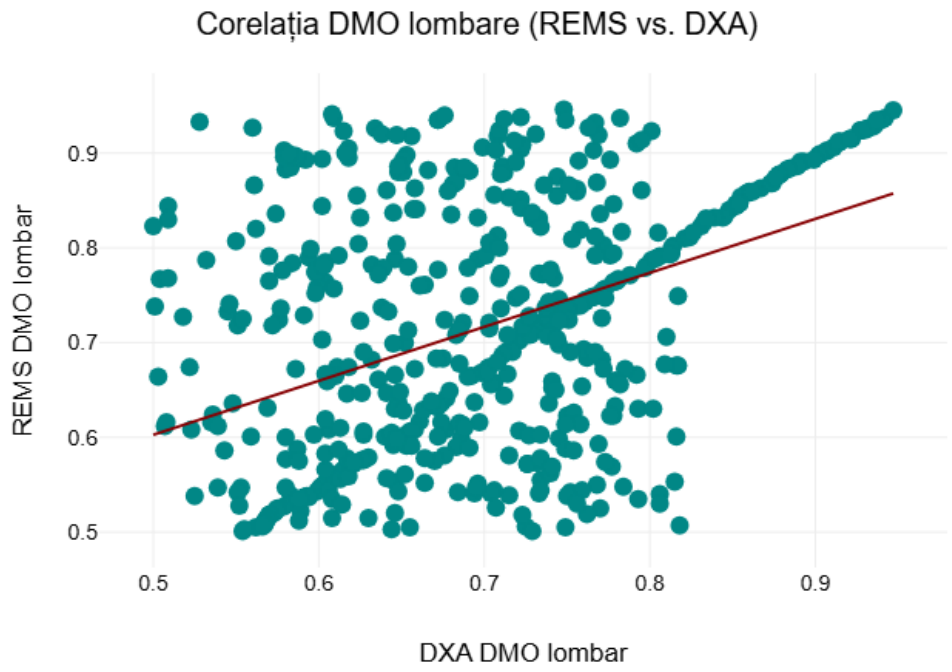

Figure 4 – The correlation between BMD measurements through DXA and REMS, which shows a good correlation for the examination of the lumbar spine. The differences may be due to the existence of structural changes specific to lumbar spondylodyscarthrosis identified in older people (Pearson, r=0.42, p<0.001).

The presence of radiological structural changes of the lumbar spine was described in 387 (72.33%) of the enrolled individuals (t-test, p<0.001), of whom 289 (74.68%) were over 45 years of age (t-test, p<0.001).

No association was found between patients' comorbidities and BMD values obtained by either DXA or REMS (Pearson[DXA] with r=0.12, p=0.654 and Pearson[REMS] with r=0.13, p=0.594). The most common comorbidities identified following the analysis of the medical file are:

- Hypertension (n=301, 56.25%);
- Dyslipidemia (n=272, 50.84%);
- Euthyroid autoimmune thyroiditis (n=57, 10.65%);
- Hypothyroid autoimmune thyroiditis controlled by Levothyroxine (n=23, 4.3%)
- Type 2 diabetes mellitus (n=15, 2.8%);
- Permanent atrial fibrillation (n=2, 0.37%).

The rest of the comorbidities described are arthritic in nature, affecting the spine and peripheral joints (hands, knees and coxo-femoris).

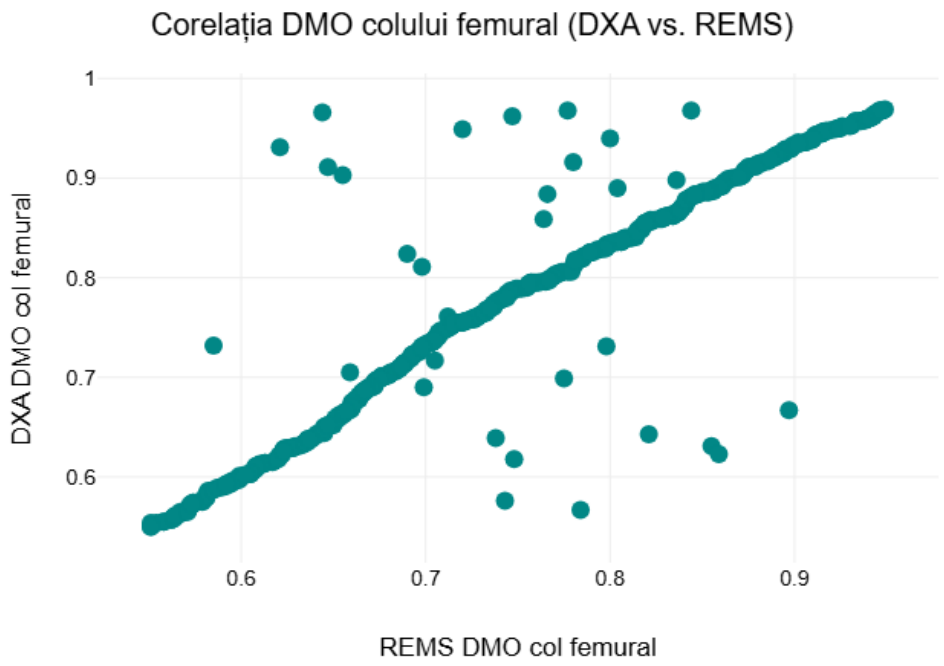

Figure 5 – Correlation between BMD measured by DXA and REMS, with a very high degree of correlation, statistically significant (Pearson, r=0.94 and p<0.001).

6. USEFULNESS OF REMS IN THE DIAGNOSIS OF OSTEOPOROSIS IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

If in the case of the control lot we have a female:male ratio of 4:1, in the case of the SpA lot this ratio is reversed. The distribution according to age is statistically equal at the level of both studied lots, as a result of the applied t-tests, statistically significant p values were not obtained. However, these aspects allow us to later compare the controls with the study group by age groups in order to observe any differences in BMD in the lumbar spine obtained by REMS.

Applying the Pearson correlation test for BMD assessments of the lumbar spine, values obtained by DXA and REMS, a high, statistically significant positive correlation is observed ($r=0.78$; $p<0.001$).

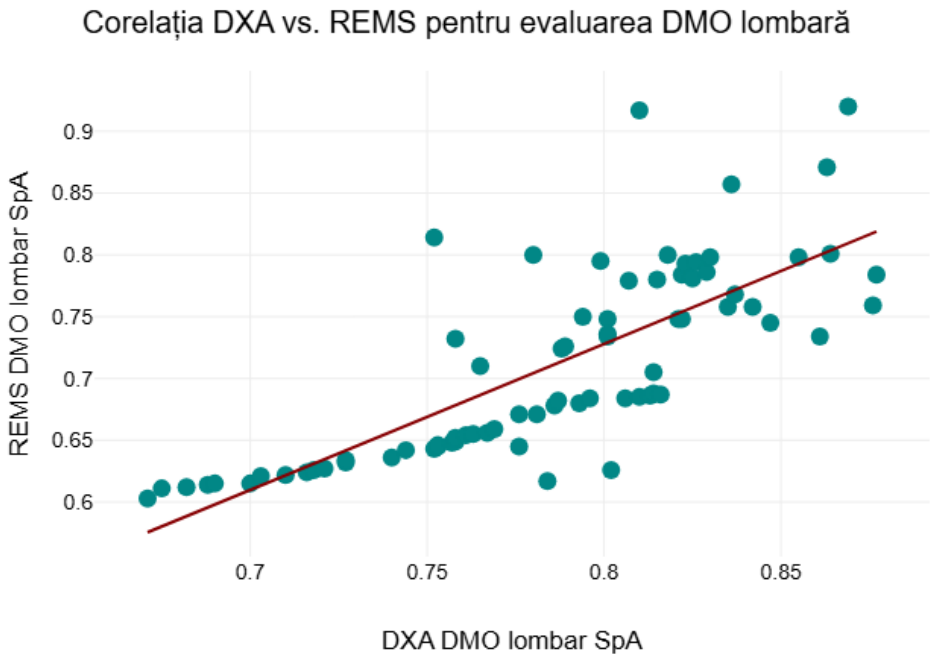

Figure 6 – Scatterdot indicating the linear correlation between DXA and REMS assessments of the lumbar spine in the group of patients with SpA (Pearson, r=0.78, p<0.001).

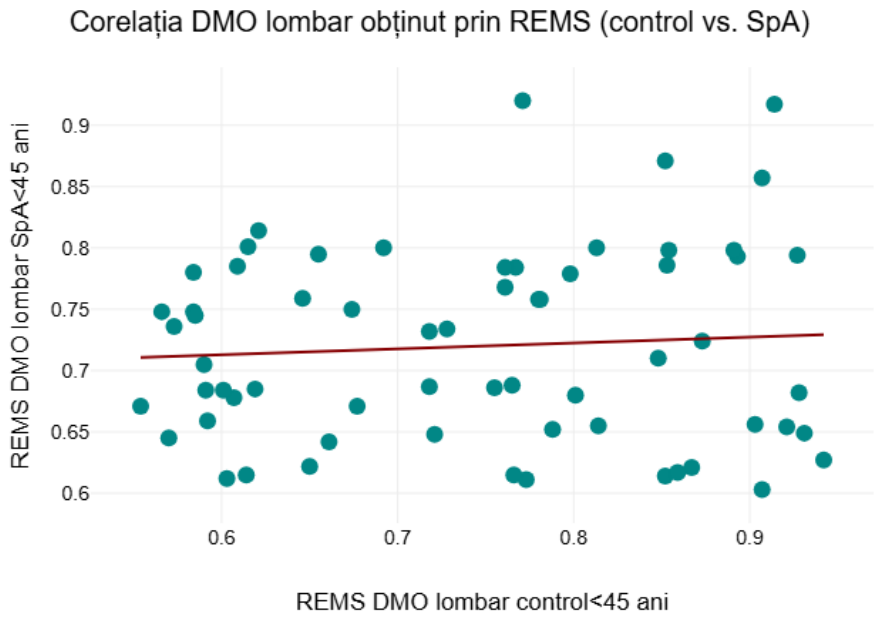

Figure 7 – Scatterplot objectifying the discrete positive correlation between the BMD control vs. SpA values, but the statistical significance was not proven (Pearson with r=0.07 and p=0.567)

The Mann-Whitney U-test analysis for lumbar spine BMD determinations between the control group and the SpA group shows that there are no statistically significant differences (p=0.223). This suggests that in young patients, with shorter duration of SpA, there are no

differences compared to individuals without SpA. Testing the Pearson correlation between the two methods did not obtain statistically significant p-values (r=0.07; p=0.567).

A Kruskal-Wallis examination followed by Dunn-Bonferroni tests were performed to be able to fully characterize the associations between the different SpA control groups and age groups. Overall, it was observed that there are overall differences between the groups studied regarding BMD measured by REMS, these differences occurring in the groups under 45 years of age and between the control group over 45 years of age and those with SpA.

Table 3 – Kruskal-Wallis analysis

Chi2	Df	p
44.34	3	<,001

Table 4 – Dunn-Bonferroni testing for age and study groups (control and SpA)

	Statistical Test	Std. Error	Std. Statistical Test	p	Adj. p
REMS lumbar BMD control<45 years - REMS BMD lumbar SpA<45 years	17.4	26.21	0.66	.507	1
REMS lumbar BMD control<45 years - REMS lumbar BMD control>45 years	102.33	16.61	6.16	<,001	<,001
REMS lumbar BMD control<45 years - REMS BMD lumbar SpA>45 years	118.01	50.89	2.32	.02	.122
REMS Lumbar BMD SpA<45 years - REMS Lumbar BMD control>45 years	84.93	24.04	3.53	<,001	.002
REMS Lumbar BMD SpA<45 years - REMS Lumbar BMD SpA>45 years	100.6	53.77	1.87	.061	.368
REMS BMD lumbar control>45 years - REMS BMD lumbar SpA>45 years	15.67	49.8	0.31	.753	1

7. UTILITY OF THE FRAGILITY SCORE (FS) IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS (axSpA)

Throughout the study, vitamin D deficiency correction was observed in the 8 patients who initially had low serum values. Prior to entering the study, a maximum of 12 months ago, 2 patients described falls from their own height, without mentioning external factors, vertigo or other identifiable clinical or paraclinical causes, rather assuming falls in the context of changes in vertebral statics. During the course of the study, no other falls were described until month 18 (visit 3).

Also, following the initial imaging investigations, 2 patients had thoracic and lumbar vertebral settlements, cases that will be discussed in detail in the following chapters. At visits 0, 1 and 2, paraclinically no biological inflammatory syndrome was detected, and at visit 3, 4 patients had biological inflammatory syndrome with CRP values between 6.43-12.24 mg/l (the normal value for the laboratory being 0-5 mg/l).

Table 5 – Descriptive statistics of the study group (t-test on single sample, p<0.001)

	Males (n=59)	**Women (n=17)**
Average age (range)[a]	37.22(20-65)	36.06(22-49)
Underweight (%)	0(0%)	0(0%)
Normal weight (%)	10(16.949%)	5(29.41%)
Overweight (%)	31(52.54%)	10(58.82%)
Obesity grade I (%)	18(30.508%)	2(11.76%)
Mild vitamin D deficiency (n=8, 10.81%)[a]	3 (5.08%)	5 (29.41%)
Participants (n=76)	**Supplement group (n=38)**	**Group without supplements (n=38)**
Initial FS	38.15(30.10-93.70)	36.589 (30.20-49.20)
VAS initial muscle strength	61.89 (10-100)	52.57 (10-100)
Initial number of falls	2	0

Although physical therapy is a common recommendation made to patients with strictly axial involvement, without biological inflammatory syndrome or without criteria for initiating biological or synthetic targeted DMARD therapies, in the case of FS no statistically significant changes were observed. Although Table 5.4.2 shows that, paradoxically, the frailty score increases in the 6 patients who underwent physical therapy, the ANOVA analysis performed later did not show statistically significant p-values (p=0.342).

At an initial glance, the statistical strength is modest in terms of supplementation. However, we are dealing with a group of 8 patients with vitamin D deficiency who can also associate significantly high values of FS. So we have chosen to analyze the impact that this deficit has on the FS. Unfortunately, we did not have data to assess how old that deficit is, due to the lack of medical documents and previous tests.

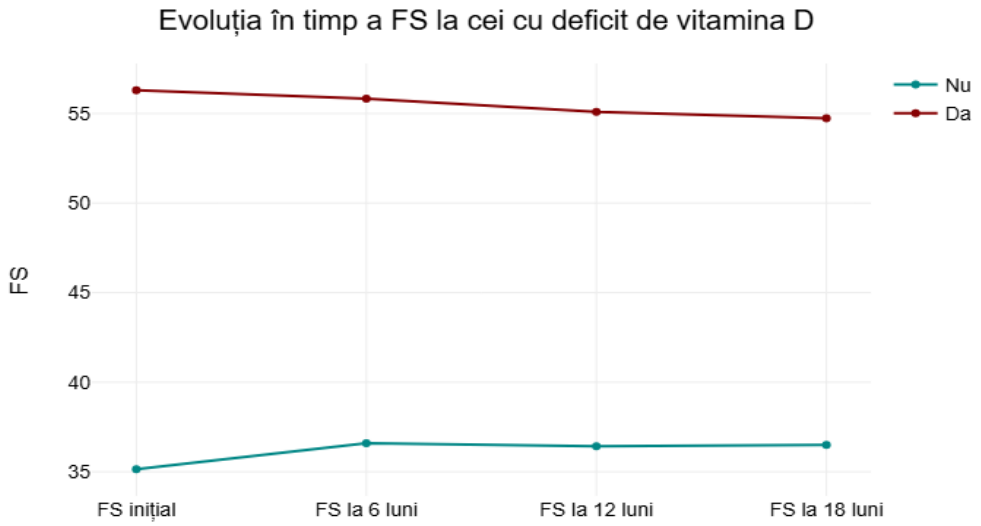

Figure 8 – Evolution over time of FS in those with vitamin D deficiency. The usefulness of supplementation becomes obvious, emphasizing the double effect of this therapy, both in correcting serum levels (with a possible influence on all metabolisms that are influenced by vitamin D), but also in correcting FS (ANOVA analysis, F[3, 222]=65.06, p<0.001).

Table 6 – ANOVA analysis following the evolution of FS over time in those with vitamin D deficiency and in those without.

	Sum of squares	Df	Mean Square	F	p	η2	η2p
Baseline FS, 6-month FS, 12-month FS, 18-month FS	72.31	3	24.1	2.81	.04	0	0.04
Vitamin D deficiency	10693.64	1	10693.64	50.54	<,001	0.38	0.41
RM Factor x Vitamin D Deficiency	35.6	3	11.87	1.38	.248	0	0.02
Residuals (Between Subjects)	15657.38	74	211.59				
Residuals (Within Subjects)	1903.03	222	8.57				

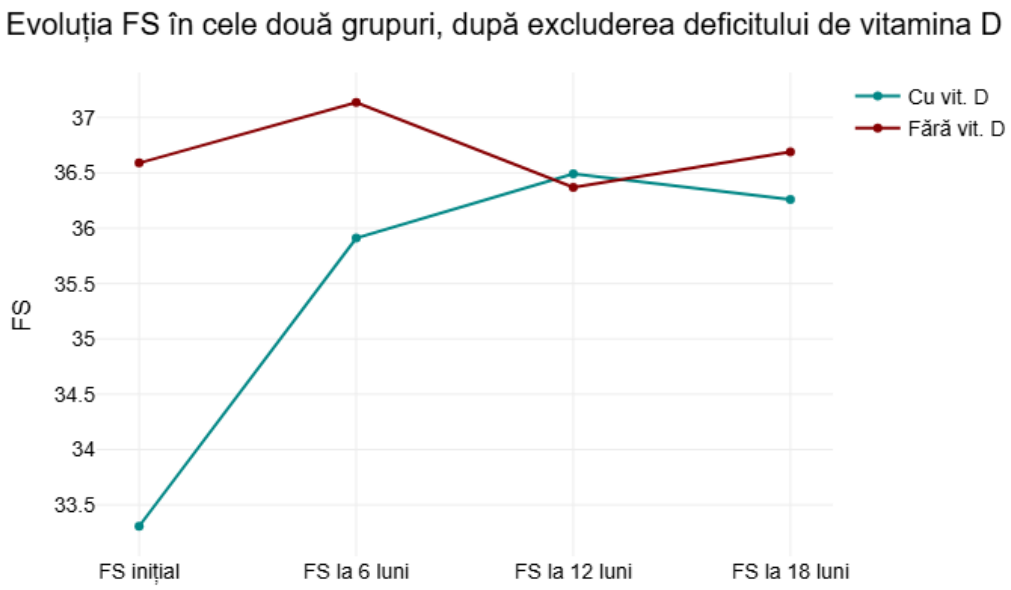

Figure 9 – Evolution between the two groups, after excluding those with vitamin D deficiency. Statistically significant differences between the two groups are not detected in this case either (ANOVA, F[1, 66]=1.07, p=0.304).

Table 7 - ANOVA analysis of the study groups after excluding those with vitamin D deficiency.

	Sum of squares	Df	Mean Square	F	p	η2	η2p
Baseline FS, 6-month FS, 12-month FS, 18-month FS	96.01	3	32	6.42	<,001	0.01	0.09
Additional groups	97.27	1	97.27	1.07	.304	0.01	0.02
RM Factor x Additional Group	111.97	3	37.32	7.49	<,001	0.02	0.1
Residuals (Between Subjects)	5977.1	66	90.56				
Residuals (Within Subjects)	986.8	198	4.98				

So far, vitamin D supplementation has a weak effect in terms of influencing the FS values measured by REMS. Regular physical therapy does not statistically significantly influence FS either. Most likely, FS is influenced by other factors, external or related to the disease itself, and further studies in this regard are necessary.

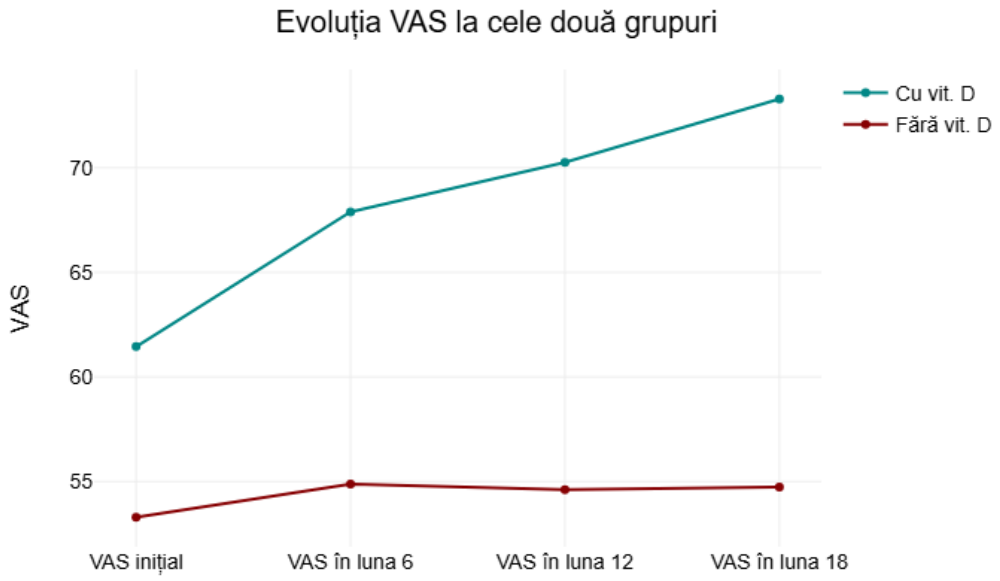

Figure 10 – Evolution over time of muscle VAS in the two groups investigated (ANOVA, F[1, 74]=7.61, p=0.007).

There is a statistically significant increase in muscle strength reported by the patient on the VAS in the group of supplements, compared to those without supplements. The ANOVA analysis confirms both the evolution of VAS over time ($p<0.001$) and the influence of vitamin D supplementation.

The Mann-Whitney U-test analysis showed no statistical link between baseline muscle VAS in patients with vitamin D deficiency and those without (*U=219, n1= 68, n2=8 p=0.375). The ANOVA analysis focused on highlighting an influence* of physical therapy on muscle VAS also did not show a satisfactory level of statistical significance ($F(1, 74)=0.2$, *p=0.657).*

8. FRAGILITY FRACTURES AS THE FIRST MANIFESTATIONS OF AXIAL SPONDYLOARTHRITIS

The onset with fragility fractures, in the absence of clinical complaints or significant paraclinical changes for axSpA represents a significant problem in the management of these cases. REMS, together with FS, are extremely useful tools in obtaining all the medical

information necessary to prescribe an appropriate and complete treatment. The use of Methotrexate should be considered in patients with axSpA and peripheral manifestations who are intolerant to Sulfasalazine or not.

Primary osteoporosis is a rare entity in middle-aged adult men. The REMS examination was not suggestive of osteoporosis, but showed BMD values in the osteopenia interval and with FS suggestive of moderately increased risk of bilateral femoral fragility fracture. Digital Hippocracy has been a challenge in terms of differential diagnosis, and further exploration is needed in the future to fully assess any impairment associated with this clinical change.

The use of Methotrexate as a form of treatment in axSpA with peripheral manifestations seems to be a good option, especially when there are contraindications to the use of Sulfasalazine or in case of insufficient disease control under this therapy. Even though Methotrexate is not mentioned in the latest ASAS-EULAR recommendations from 2022, the RCA still recommends its use. Some studies have shown a favorable evolution in ankylosing spondylitis (AS) with regard to the clinical manifestations and control of biological inflammatory syndrome.

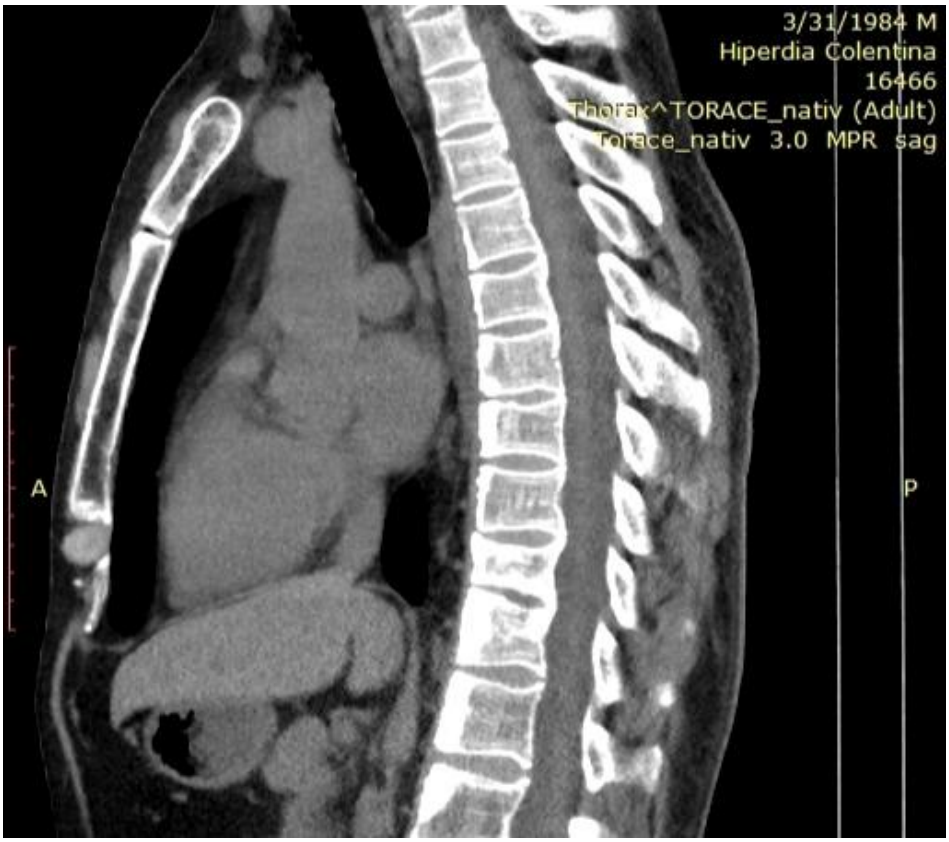

Figure 11 – Image obtained during the pulmonary hrCT evaluation showing the structural changes of the thoracic spine, with the presence of syndesmophytes and posterior syndesmophytic bridges and verbral settlements at the lower thoracic level.

9. STUDY ON THE EFFECT OF DISEASE-MODIFYING ANTIRHEUMATIC MEDICATIONS

The descriptive analysis showed a higher frequency of inflammation in the group of patients without treatments and in those taking NSAIDs alone, compared to DMARD therapies ($p<0.001$).

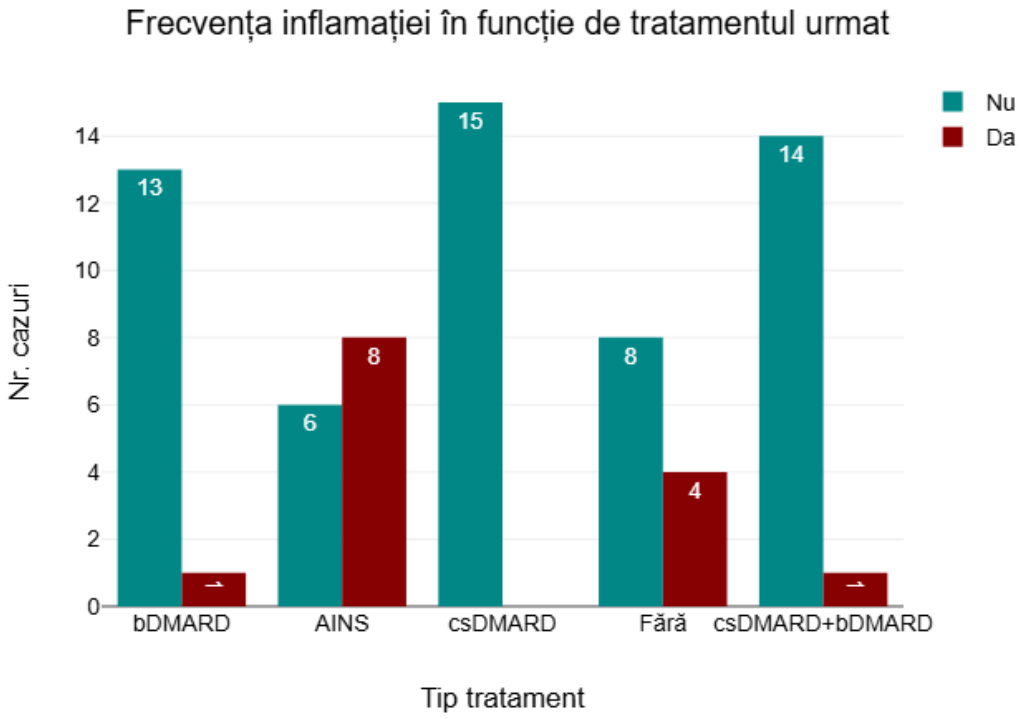

Figure 12 – Distribution of biological inflammatory syndrome among treatment groups.

After describing the batches in terms of inflammation and the therapies followed, it is important to evaluate the validity of the REMS method of assessing BMD. Thus, Pearson's correlation analysis showed a very high correlation between lumbar and femoral BMD measurements in all study participants ($r=1$, $p<0.001$).

ANOVA analysis showed no significant differences between BMD values measured by REMS ($F[1, 68]=0.98$, $p=0.326$). However, statistically significant differences were identified in the difference between lumbar and femoral BMD depending on the type of pathology, suggesting that the type of involvement, axSpA or PsA, directly influences BMD values ($F[1, 68]=5.58$, $p<0.001$).

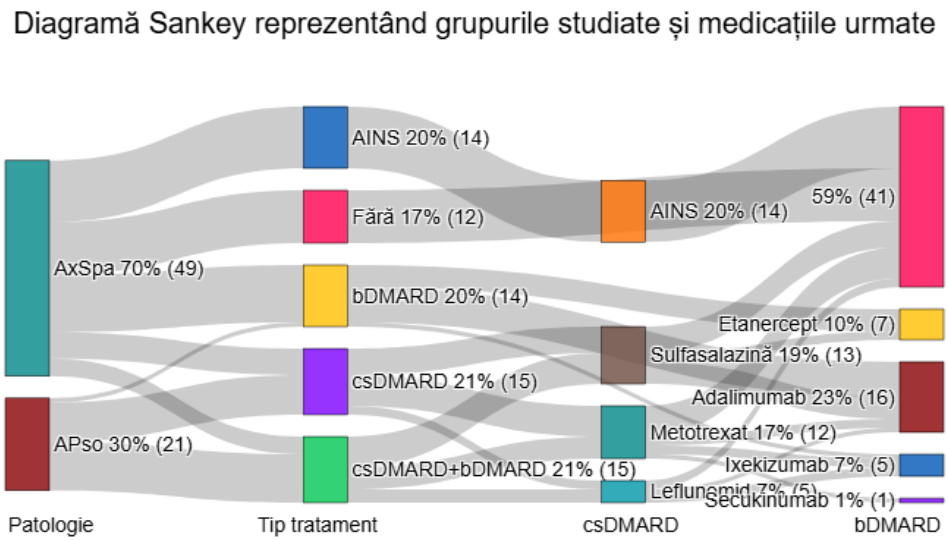

Figure 13 – Diagram representing the groups studied and the treatments followed. All groups show a relatively uniform distribution on different treatment arms.

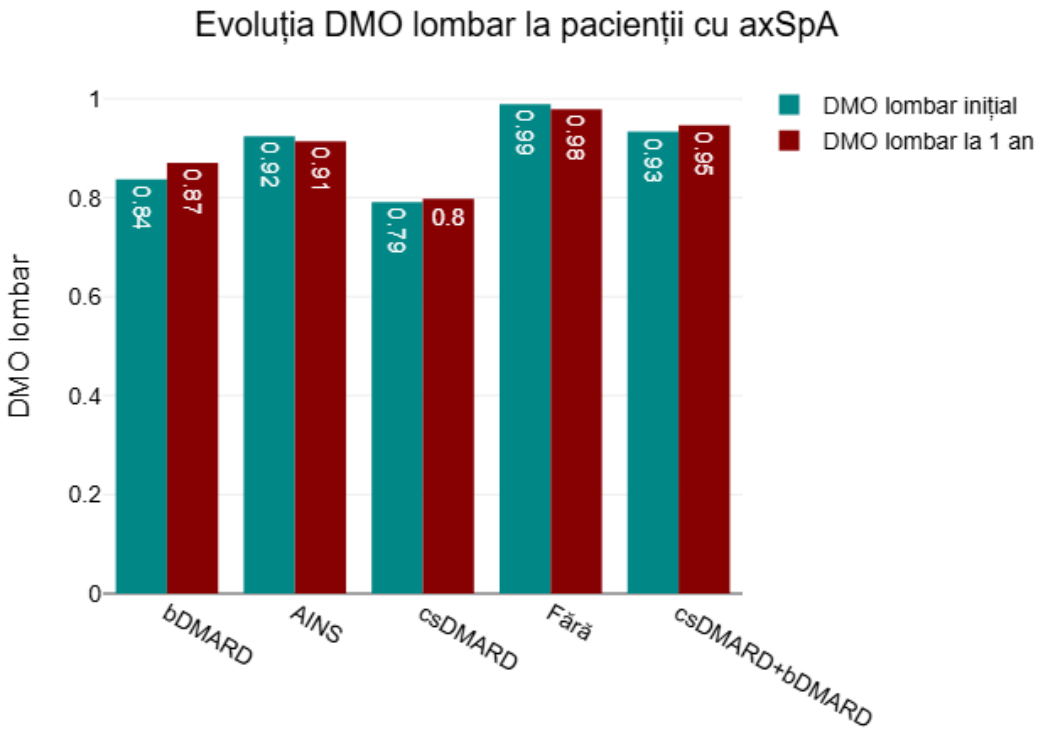

Figure 14 – Differences within the axSpA group (ANOVA, p<0.001).

Table 7.4.15 – ANOVA analysis of lumbar BMD evolution in patients with axSpA.

	Sum of squares	Df	Mean Square	F	p	η2	η2p
Baseline lumbar BMD, 1-year lumbar BMD	0	1	0	7.73	.008	0	0.15
Treatment type	0.38	4	0.09	3.4	.016	0.23	0.24
MRI Factor x Treatment Type	0.01	4	0	23.44	<,001	0.01	0.68
Residuals (Between Subjects)	1.22	44	0.03				
Residuals (Within Subjects)	0	44	0				

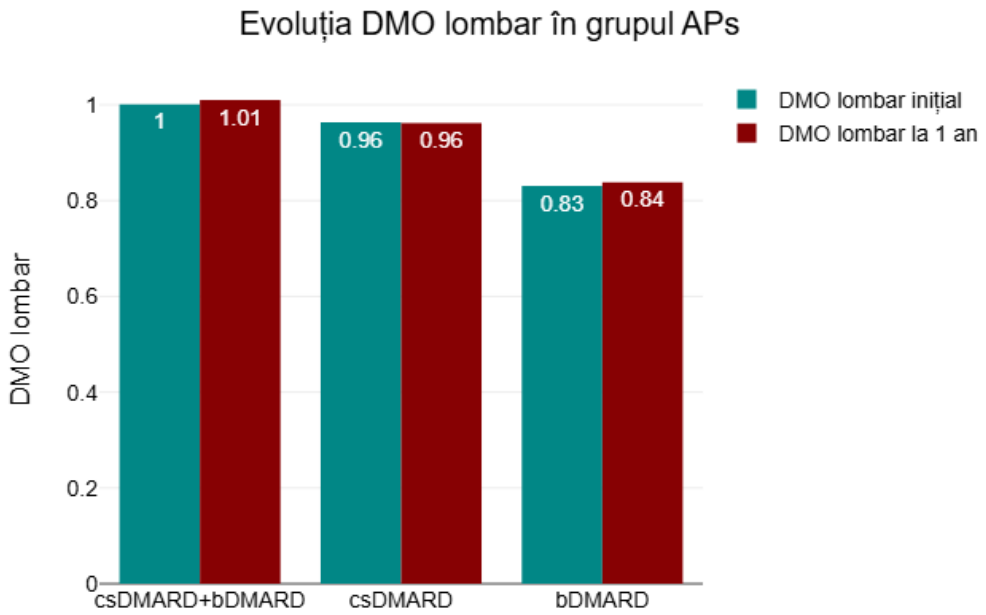

Figure 15 – Evolution of lumbar BMD in patients with PsA (ANOVA, p<0.001).

Table 7.4.16 – ANOVA analysis of the evolution of lumbar BMD under treatment in the group of patients with PsA.

	Sum of squares	Df	Mean Square	F	p	η2	η2p
Baseline lumbar BMD, 1-year lumbar BMD	0	1	0	19.42	<,001	0	0.52
Treatment type	0.06	2	0.03	0.89	.427	0.09	0.09
MRI Factor x Treatment Type	0	2	0	14.41	<,001	0	0.62
Residuals (Between Subjects)	0.62	18	0.03				
Residuals (Within Subjects)	0	18	0				

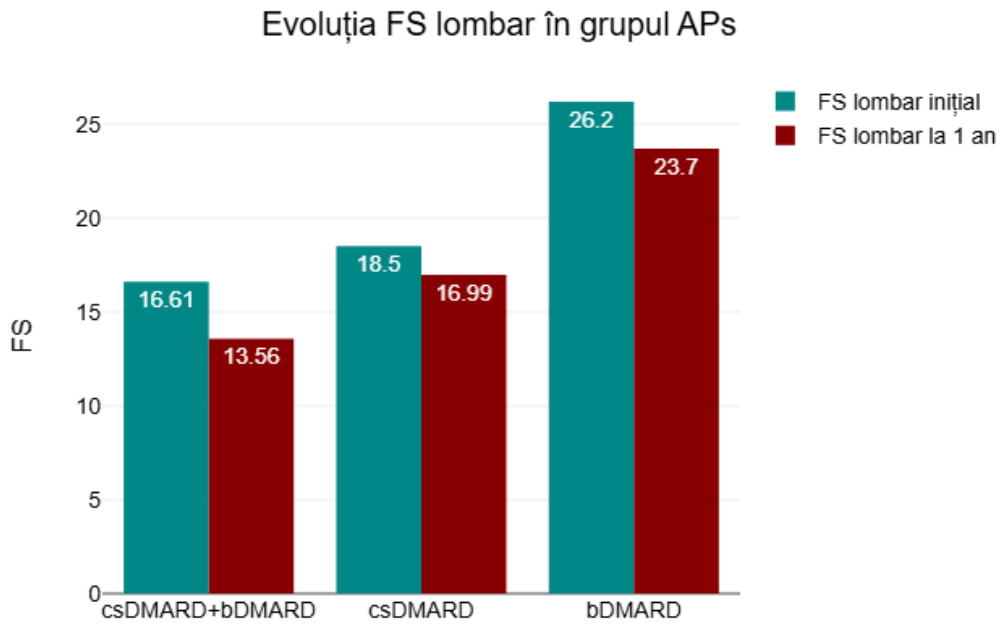

Figure 7.4.15 – Evolution of FS in the group of patients with PsA (ANOVA, p<0.001).

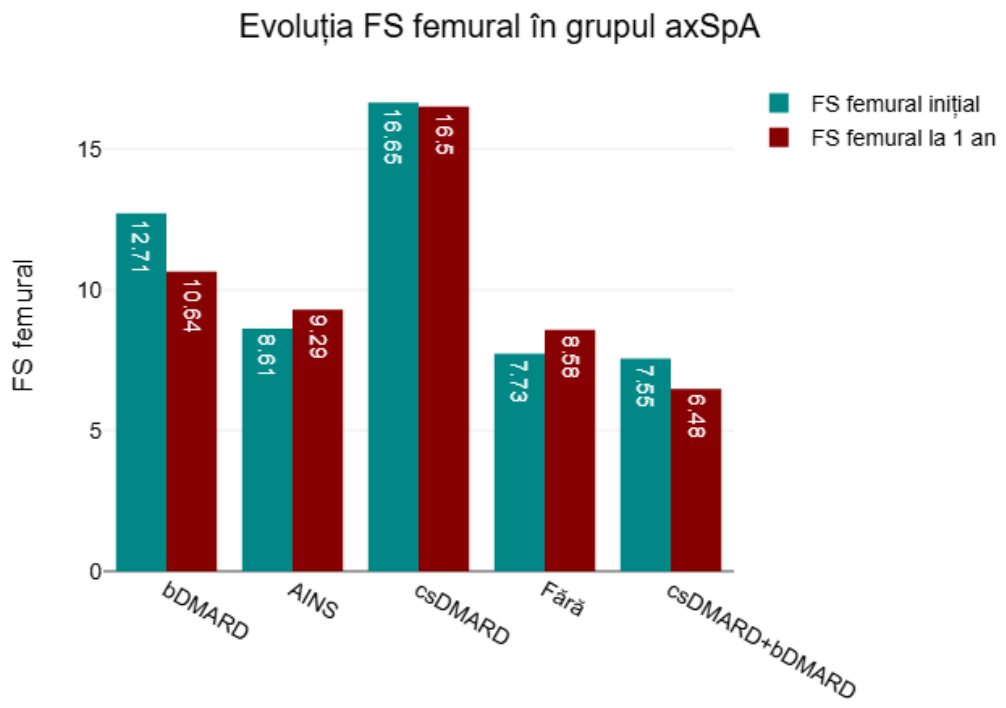

Figure 7.4.18 – Evolution of femoral FS in the AxSpA group (ANOVA, p<0.001).

10. FINAL CONCLUSIONS

Radiofrequency Echographic Multi-Spectrometry (REMS) is an efficient and fast method of assessing bone density. This provides the possibility to obtain information related to bone mineral density (BMD), T score and frailty score.

During the complex evaluations carried out during the work and with the inclusion of diverse populations, in different clinical contexts, we were able to demonstrate that this technique deserves to be used more often in clinical practice. The non-inferiority of the method compared to the current gold standard in the evaluation of BMD, allows its use in almost any context.

First of all, we have demonstrated that REMS can be used in young patients, without risks associated with irradiation, even if this dose is low, for the general population assessment and to provide insights into the factors that can influence the achievement of a peak bone mass as high as possible. We initially assumed, after researching the literature, that diet and physical activity can significantly influence the degree of bone mineralization. We have proven that their role is minimal compared to the studied population and genetic traits, especially weight and body mass index (BMI).

We then focused on comparisons of REMS with dual X-ray absorptionmetry (DXA), the gold standard in everyday medical practice, on a significant population in order to perform a

statistical analysis as accurate as possible. We demonstrated that there are no significant differences between the two techniques in terms of obtaining BMD data and correct classification in the groups of normal, osteopenia and osteoporosis. We also concluded that in certain clinical situations, REMS could be a faster evaluation option compared to DXA, due to the possibility of performing the analysis during the clinical presentation of the patient in the hospital or during a medical consultation, not requiring an appointment in medical centers specialized in the diagnosis of DXA.

Data in the literature are extremely poor regarding the use of REMS in patients with axial spondyloarthritis (axSpA). We compared the particularities of bone mineralization between them and the population group investigated previously. We have demonstrated that REMS provides accurate and accurate data here too. At the same time, we confirmed the data from the medical literature on the risks of osteoprosy in axSpA, demonstrating that the truth about the prevalence of bone pathology in these patients is in the middle, not at the two extremes. Also, the lack of a very large difference between the control group and the recently diagnosed axSpA group was not as large as speculated in other clinical trials.

Of course, noticing the lack of any significant risk associated with these axSpA patients, we decided to test the new software of the method, the one related to the calculation of the frailty score (FS). It allows the assessment of bone fragility, independent of BMD, based on radiofrequency waves and spectral analysis, just like the basic principle of REMS, but the spectrum obtained is compared with the data collected during numerous investigations on patients with different degrees of bone architectural degradation. Thus, we conducted a prospective study in which we aimed to evaluate the evolution of FS in the context of vitamin D supplementation in the same group of patients diagnosed with axSpA and to highlight whether there is any effect of this supplementation on the risk of frailty. We chose to place patients with immediate deficiency in the supplemental arm, the rest of the group randomizing it into the two arms, with supplemental and without supplementation. We noticed that there is indeed a benefit of vitamin D supplementation, mainly in patients who had initial deficiency, respectively in those who had high values of the initial FS. Also, the usefulness of vitamin D in axSpA is not obtained immediately, but by administration over time, stopping the demineralization rate and reaching a plateau of the FS during the evaluations.

We later chose to present a case of special interest. A patient, middle-aged adult, with no previous inflammatory vertebral pain, but who had multiple vertebral compaction during lifting a heavier weight above the shoulders. This case again demonstrated the validity and usefulness of REMS and FS in the evaluation of bone mineralization and determination of bone fragility. This evaluation allowed from the very beginning to make a quick medical decision that over time proved to be correct, that of supplementing with vitamin D and not initiating an anti-osteoporotic treatment. Also, this case fit perfectly into the context of the current work, as the patient was diagnosed with axSpA. In addition, this case demonstrated that the ASAS recommendations for treatment of axSpA with peripheral manifestations are not absolute rules

to follow regarding the use of Sulfasalazine in these cases. Consultation of other international treatment guidelines has shed light on the possibility of using Methotrexate, which, in this case, has proven to be a life-saving treatment, which interrupted the persistent biological inflammatory syndrome, providing a good evolutionary prognosis for this patient. Also, by comparing this case with another briefly described, represented by the brother of the first patient followed, it strengthens the data in the literature on the genetic and pathogenic polymorphism of diseases in the spondyloarthritis group.

Finally, we chose to determine whether the therapies commonly used for the treatment of axSpA and psoriatic arthropathy (PsA) have any effect on BMD, lumbar and femoral T and FS scores. In this case too, we designed a prospective study, in which we used REMS to determine all the indices tracked. We demonstrated that there is a statistically significant relationship in both groups studied between the treatment followed and the evolution of bone health indices. Biological therapies (bDMARDs) as well as combined therapies with conventional synthetic and biological medications (bDMARD+csDMARD) showed improved markers compared to those without treatment, with non-steroidal anti-inflammatory therapy or with csDMARD treatment alone. We also emphasized that these are not targeted treatments to increase bone density or improve bone fragility, but rather should be considered preventive treatments for progression to osteopenia, osteoprosis and fragility fractures in patients with axSpA and PsA.

As mentioned before, the last study is still ongoing, but, due to time constraints, we chose to partially present these results, and at the end of the study, the results will materialize in the publication of an article in a large international journal. Also, throughout the work, there were delicate financial situations, related to the lack of obtaining a grant, which inevitably led to the difficulty of publishing the results in international journals, as we initially planned. There were no external sources of funding, all costs being borne personally (processing, medications, correction of manuscripts sent for publication and the actual publication).

Research on the usefulness of REMS and FS must inevitably be continued, and the results of future studies made public at international level. Also, the inclusion of other rheumatic inflammatory pathologies is the main priority at this time, as they are frequently associated with osteoporosis and bone microarchitectural changes that can significantly decrease the quality of life of patients with these conditions.

Last but not least, European and international collaboration networks must be created to be able to gather large numbers of patients, from different geographical areas and with different genetic characteristics in order to be able to paint a complete and correct picture of this procedure.

However, we finally managed to demonstrate what we initially set out to do, namely to show the usefulness of REMS in the diagnosis of osteoporosis in patients with spondyloarthritis, and not only.

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