"OVIDIUS" UNIVERSITY CONSTANTA

FACULTY OF MEDICINE

MORPHOLOGICAL, CLINICAL AND IMAGING CHARACTERISTICS OF THE HANDS' SMALL JOINTS IN SEROPOSITIVE AND SERONEGATIVE RHEUMATOID ARTHRITIS

- ABSTRACT -

SCIENTIFIC COORDINATOR:

PROF. BORDEI PETRU

PhD STUDENT:

OPREA DOINIŢA

Constanta

2012

TABLE OF CONTENTS

INTRODUCTION

Rheumatoid arthritis, encountered in the specialty literature as chronic progressive polyarthritis, is a chronic inflammatory disease that typically affects the small and medium joints with symmetrical distribution. Although the main events are at a musculoskeletal level, rheumatoid arthritis can affect any organ or system of the human body, and therefore the term "*rheumatic disease*" would probably be more appropriate for this condition.

Hippocrates first described a disease similar to rheumatoid arthritis as "*arthritis that usually occurs around the age of 35 years*" and Galenus first used the term "*rheumatismus*" in the 2nd century BC.

The first detailed description of the rheumatoid arthritis was made within the MD thesis of Augustine Jacob Landrė Beauvais, held at the University of Paris in 1800. It concluded that he had not found convincing evidence for the existence of rheumatoid arthritis in Europe long before 1800. Landrė Beauvais used the term "*primary aesthenic gout*" to describe the rheumatoid arthritis. Charcot named the same disease "*rhumatisme articulaire chronique*" in his MD thesis in 1853. In 1848 Sir Alfred Garrod discovered crystals of uric acid and he was able to distinguish the gout from what he proposed in 1859 to be called "*rheumatoid arthritis*".

The British Ministry of Health adopted the term "*rheumatoid arthritis*" in 1922. The term was taken over by the American Rheumatology Association (ARA) in 1941 and by the International League Against Rheumatism (ILAR) in 1957. In 1954, when John Lawrence became the first director of the Arthritis Research Campaign Epidemiology Unit, the "*rheumatoid arthritis*" terminology was well established.

Rheumatoid arthritis is the most common inflammatory joint disease, affecting 0.5-1% of the world population. Although global prevalence is constant, it can vary depending on geographic location and race.

The diagnosis of rheumatoid arthritis is determined by history, physical examination, laboratory tests and after other diagnoses suspicions were excluded.

Most patients have a fluctuating chronic course of the disease, which untreated leads to progressive joint damage, irreversible, with permanent deformation, accompanied by functional impairment and reduced life expectancy.

The severity of the disease results from the fact that over 50% of patients stop working during the first 5 years of disease, and in 10% of cases there is a serious disability during the first two years of evolution. The arrival of some visceral lesions is responsible for shortening the average life period of 5 to 10 years. Rheumatoid arthritis is thus not only a major medical problem but also a social problem of public health.

We considered appropriate to draw up a comparative study, a descriptive-retrospective one, on various aspects of rheumatoid arthritis, given the clinical and social importance of this condition.

THE PERSONAL PART

MATERIAL AND METHOD

In order to obtain an appropriate evolution of the present research, there have been used a number of methods which have provided the scientific basis of the debated topic and which were used while taking, recording and processing of data, as well as while interpreting the results.

PATIENTS AND STUDY SELECTION PROCEDURE

This clinical study is a comparative and descriptive-retrospective one, held within the Department of Rheumatology of the Medical Clinic 3 belonging to the Constanta County Emergency Hospital in 2007-2009.

The personal observation sheets and documentation of patients were used as working material, selecting in this way 66 patients suffering from seropositive and seronegative rheumatoid arthritis.

The selected patients were reviewed in terms of diagnosis validity according to the ACR criteria 1987, confirming in this way the previous diagnosis of rheumatoid arthritis. Thus, the study included patients from Constanta county, meaning those with definite diagnosis of rheumatoid arthritis (diagnosis established for at least 2 years), including both forms of the disease: seropositive and negative. Patients diagnosed with chronic hepatitis B or C (including those with undetectable viremia) were excluded, as well as those with fibromyalgia, paraneoplastic syndromes, psoriasis, and those with other chronic diseases that affect the joints (SLE, gout / pseudogout, scleroderma, spondylarthropathies, sarcoidosis, reactive arthritis or Lyme disease).

The 66 eligible patients, after signing the informed consent (Appendix 1) were divided into two groups: a group of seropositive RA and another seronegative.

During the visit (that had as purpose their inclusion in the study) the completion of inclusion criteria and the absence of the exclusion ones was intended; the patients demographics were obtained, as well as their medical history and clinical examination; questionnaires assessing disease activity were filled up and blood samples were collected for laboratory analyses.

Table 7. Items of interest for patients in the study.

PATIENTS'PERSONAL DATA	AIMED VARIABLES
Demographics and psychosocial	Age, sex, area of residence, ethnicity, social integration, education level
Family history	Family history of autoimmune diseases, rheumatic diseases or cancer
Pathological personal history	Data regarding the underlying disease
	Extra-articular manifestations
	Cardiovascular comorbidities
Previous and current treatments	Corticosteroids Background treatments
Anamnestic data from the beginning	Morning stiffness
	Pain score - VAS
	The number of tender joints
	The number of swollen joints
	The presence of rheumatoid syndrome
Data from the pacient's documentation	Biological data from the beginning: ESR, CRP, Hb
	Immunological tests performed: RF, anti-CCP antibodies
	ANA
	Imaging data performed: X-rays, ultrasound, MRI of hands
Clinical examination - assessing signs of active TMD	The number of tender and swollen joints
	Morning stiffness
	Pain score - VAS
	DAS 28
	CDAI
	SDAI
Laboratory tests	Complete blood test
	ESR, CRP
	Rheumatoid factor (RF)
	anti-CCP antibodies
	ANA
Evaluation of mechanical articular status	Joint mobility The presence of deformation / joint ankylosis in the hands
Evaluation of the disease status	Radiological staging - Steinbrocker O.
Identification of extra-articular manifestations	General clinical examination
	Cardiac examination
	Ophthalmological examination
	Pulmonary X-ray
Evaluation of joint damage assessment	Hands radiography
	Hands-on musculoskeletal ultrasound
	MRI hands
Evaluation of functional status and quality of life	Lee functional index; Functional classification Steinbrocker; HAQ.
Image evaluation of sesamoid hand bone	Hands radiography 2D and 3D reconstructions performed on computed tomography

DATA STATISTICAL ANALYSIS:

- ***χ^2 comparison test (association).***

A. Correlation values at nominal level:

1. φ coefficient: $\varphi = \sqrt{\frac{\chi^2}{n}}$

2. C coefficient: $C = \sqrt{\frac{\chi^2}{n + \chi^2}}$

3. V coefficient: $V = \sqrt{\frac{\chi^2}{n(q-1)}}$

4. λ coefficient:

B*. Correlation values at ordinal level:*

1. Goodman and Kruskal's γ coefficient:
2. Somer's *d* coefficient:
3. Kendall's τ_b coefficient:

RESULTS AND DISCUSSION

SPECIFIC ISSUES OF THE SESAMOID BONES IN RHEUMATOID ARTHRITIS

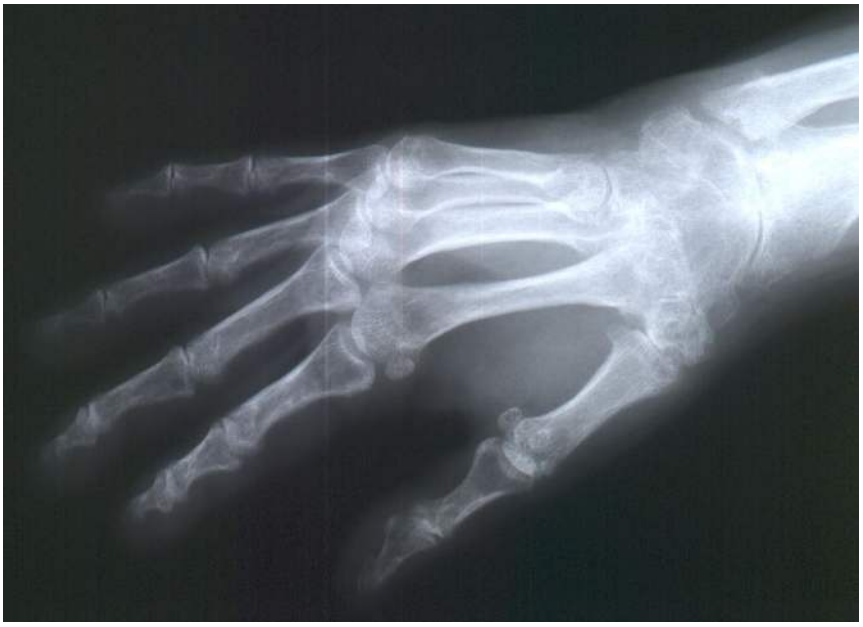

Fig. 9 – The right hand: 3 sesamoid bones (lateral, the smallest, anterior and medial), in the metacarpal head I; lateral sesamoid at the level of the index

At the level of the metacarpophalangeal joint of the thumb I have found 26 cases (47.27% of the sesamoid bones of the thumb), only 9 cases (16.36% of the sesamoid bones of the thumb) strictly corresponding to the joint spacing. In 29 cases (57.73% of them), the sesamoid bones were located in the metacarpal head I, therefore over the joint spacing. The situation of an only one sesamoid in the thumb was met within 21 cases (38.18% of the sesamoid bones of the thumb), the most common being located medially, in 9 cases (16.36% of them), on the anterior part, 7 cases (12.73%) and in 5 cases (9.09%) the sesamoid was located on the lateral side.

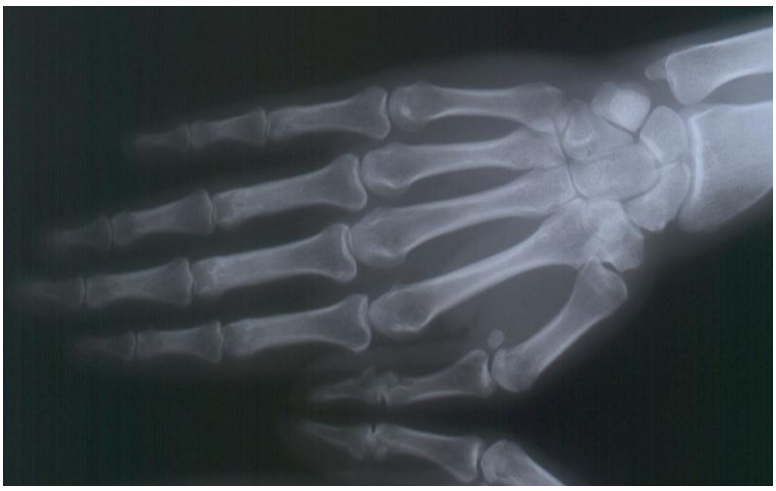

Fig. 8 – An oval sesamoid (sesame seed) at the level of the right hand medially situated at the level of the metacarpophalangeal joint of the thumb; two oval sesamoid bones medially located at the interphalangeal joint of the left hand's thumb.

Two sesamoid bones were met in 60% of the sesamoid bones of the thumb being placed most commonly medially and anterior, aspect found in 30.91% of the sesamoid bones of the thumb, 18.18% of the sesamoid bones of the thumb being medially located, as a result of their pathological dislocation. In 10.91% of the sesamoid bones of the thumb, one was medially located and the other one lateral, so the Rouvière quoted version was met by me as having the lowest percentage.

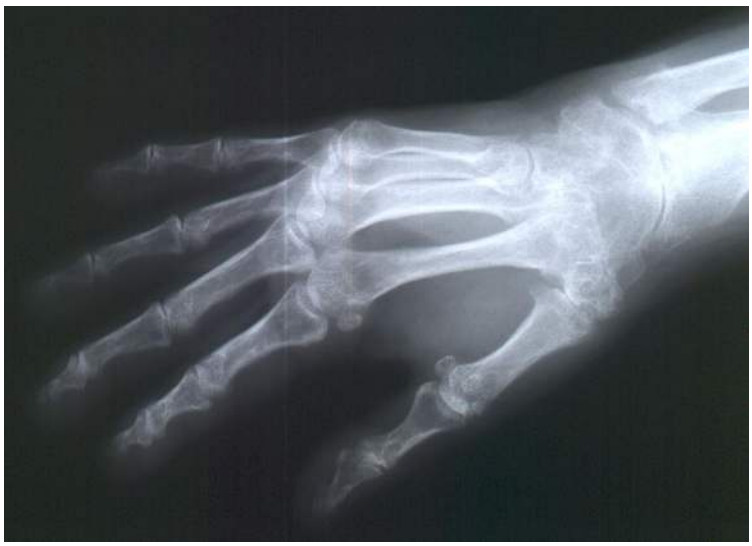

Fig. 9 – The right hand: 3 sesamoid bones (lateral, the smallest, anterior and medial), in the metacarpal head I; lateral sesamoid at the level of the index

In one case, I met three sesamoid bones, an aspect not quoted by any author of the ones I had the possibility to consult. Rouvière quotes the presence of the sesamoid bones in the other metacarpophalangeal joints, more common at the index and auricular level. I have met only 2 cases (3.33% of cases) in which a sesamoid

bone was present on the lateral side of the index, without finding any other case at the level of the other fingers. Rouvière cites the possible presence of rare sesamoid bones at the level of the interphalangeal joint of the thumb, aspect that I have met in 3 cases (5% of cases), the sesamoid bones being located in the middle of the interphalangeal joint.

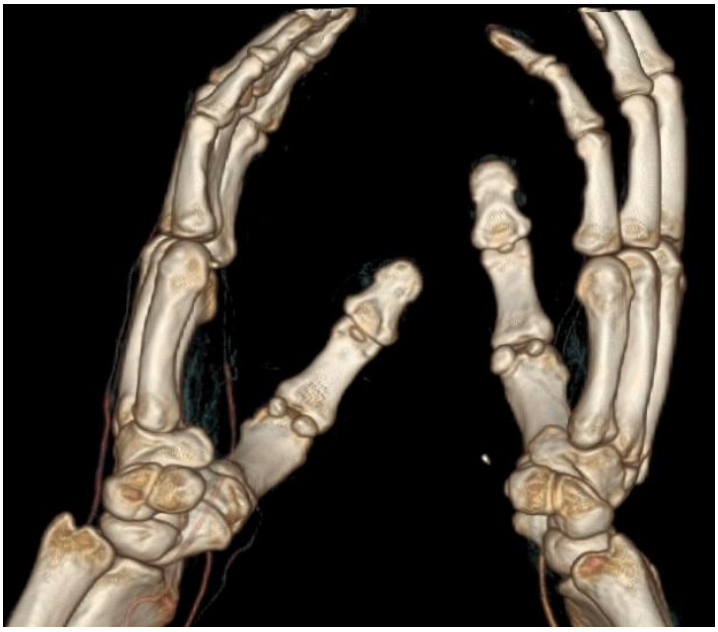

Fig. 12 – The right hand: 2 sesamoid bones, lower medial and lateral oval round and bulky, located at the interlining of the metacarpophalangeal joint of the thumb; oval transverse sesamoid bone situated in the middle of the interphalangeal joint of the thumb. The left hand: 2 sesamoid bones located at the interlining of the metacarpophalangeal joint of the thumb: the lateral, oval and bulky, the average one being round; oval transverse sesamoid bone situated in the middle interphalangeal joint of the thumb.

For Rouvière and Picioruş the sesamoid bones have a sesame seed form, Rouvière offering a rounded shape for the medial sesamoid bone and an oval shape for the lateral one. I have found more frequently the oval shape in 50% of cases, in 45% of cases, and in 5% of cases the semilunar form was met, unquoted in the specialty literature. I have not met the presence of sesamoid bones in 9 cases.

CLINICAL AND IMAGING SPECIAL CONSIDERATIONS OF THE HANDS' JOINTS WITH RHEUMATOID ARTHRITIS PATIENTS

I have analyzed the data of 66 patients with rheumatoid arthritis, divided into two groups: seronegative (group A) and seropositive (group B).

Demographics - distribution by sex:

Analyzing the demographics of patients included in the study, female sex predominance is noted in a percentage of 89.39%, males being represented in a proportion of only 10.61%.

Table 15. Distribution of RA patients according to sex.

Sex	No of patients	Percentage
Male	7	10.61
Female	59	89.39

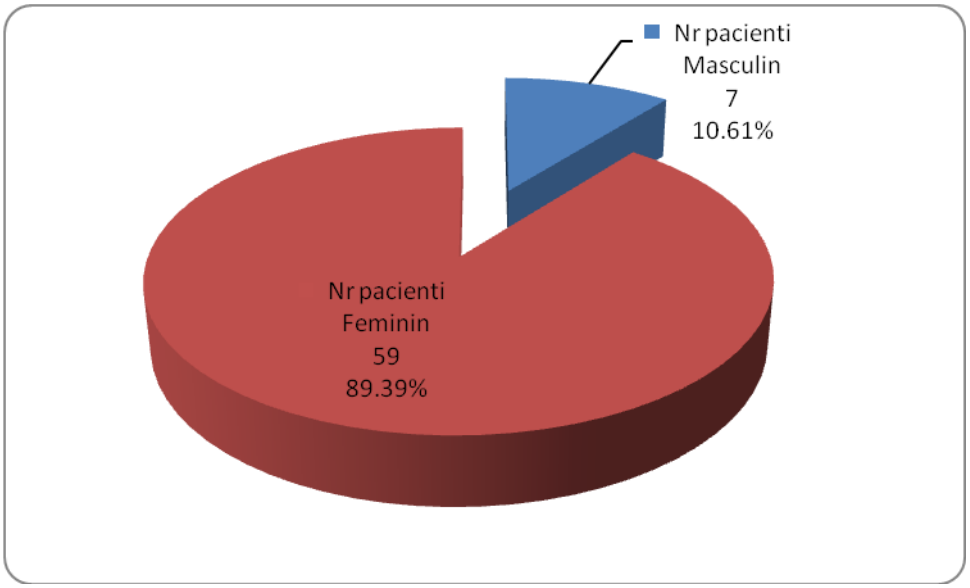

Chart 1. Distribution of RA patients according to sex.

Table 16. Distribution of seropositive and seronegative RA patients according to sex.

Sex	Group A	Percentage	Group B	Percentage
Male	4	19.05	3	6.67
Female	17	80.95	42	93.33

There is a higher frequency of females in both forms of the disease (seropositive and seronegative) and in terms of male gender the distribution is roughly equal between the two groups.

Demographics - distribution according to age:

Depending on the distribution by age, it was found that most patients with rheumatoid arthritis are over 50 years in both groups, whereas in the age group 30-50 years, there is a statistically significant difference between group A and group B of 19.05% and 6.67% respectively. Not eligible for the study were patients younger than 30 years.

Table 17. Distribution of RA patients according to age.

Age	Group A	Percentage	Group B	Percentage	Total
0-30 years	0	0.00	0	0.00	0
30-50 years	4	19.05	3	6.67	7
over 50 years	17	80.95	42	93.33	59
Total	21	100	45	100	66

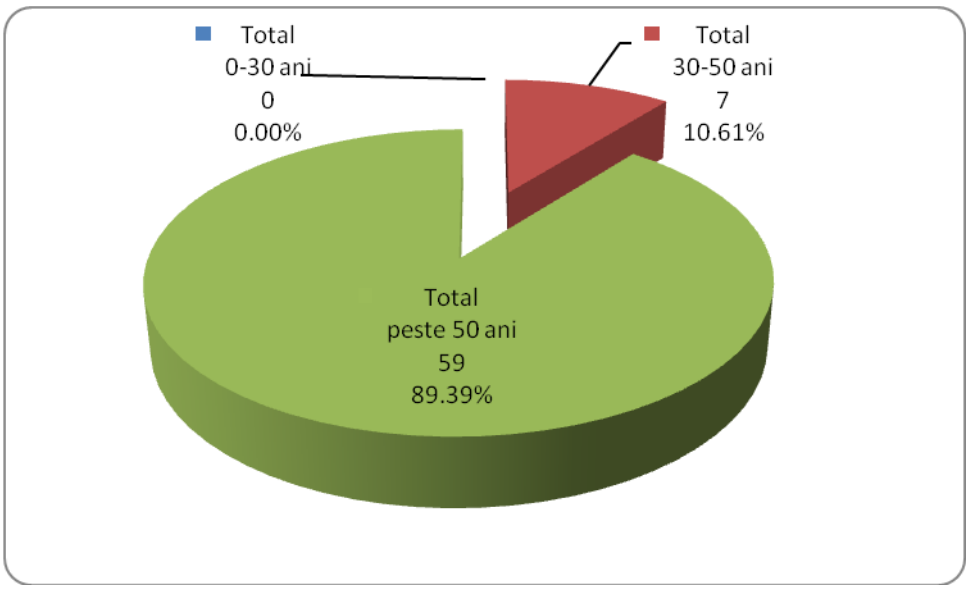

Chart 3. Distribution of RA patients according to age.

We note the fact that in our study 89.39% the age of the patients is between 51 and 85 years.

Social characteristics - distribution by area of origin:

Most patients included in the study come from urban areas; they are represented by a percentage of 69.70%, versus 30.30% patients living in rural areas. One possible explanation for the greater frequency of urban patients is the fact that these patients have a clear advantage in terms of access to information, have more opportunities to investigate and establish early diagnosis and therapeutic regimen.

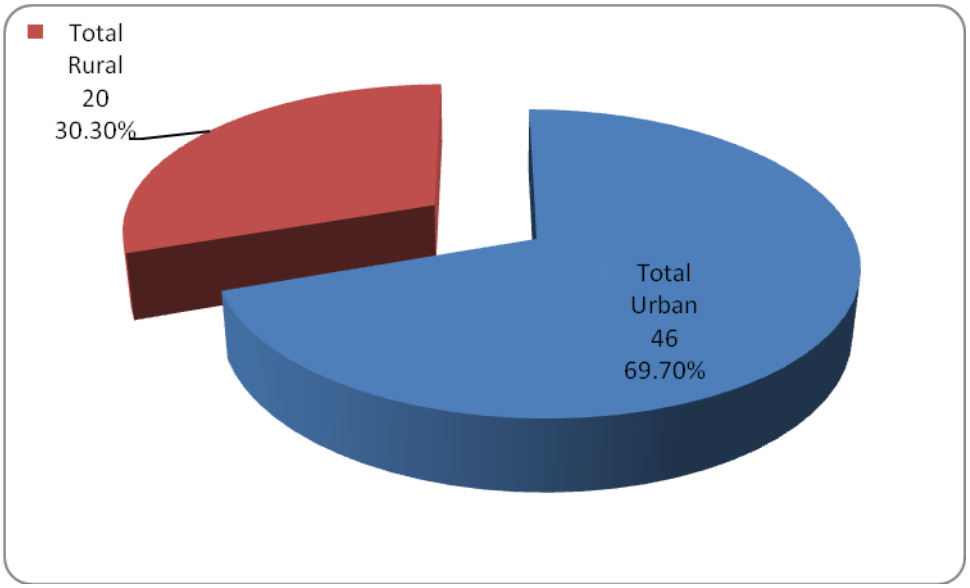

Chart 5. Distribution of RA patients according to area of origin.

Table 18. Distribution of RA patients according to area of origin.

Background	Group A	Percentage	Group B	Percentage	Total
Urban	16	76.19	30	66.67	46
Rural	5	23.81	15	33.33	20
Total	21	100	45	100	66

Social characteristics - distribution according to social integration:

The groups were analyzed in terms of social integration and statistically significant results are noted within the group of seropositive rheumatoid patients (group B); thus, the rate of disabled patients, as well as the medically retired ones is considerably higher among the seropositive patients, the unemployment rate being approximately equal. One can also notice a greater frequency of employees in the group of seronegative patients.

Table 19. Distribution of RA patients according to social integration.

Background	Group A	Percentage	Group B	Percentage	Total
Handicap	4	19.05	6	21.02	10
Unemployed	1	4.76	1	2.22	2
Retirement age	7	33.33	18	33.55	12
Medically retired	4	19.05	12	37.44	14
Employee	5	23.81	8	17.77	26
Total	21	100	45	100	64

Social characteristics - distribution by ethnicity:

Romanian ethnic predominance was found both in seropositive and seronegative forms. Within the seropositive form of the disease (group B) an equal polyarthritis frequency (15.56%), both related to Aromanian patients and Muslims was highlighted.

Table 20. Distribution of RA patients by ethnicity:

Age	Group A	Percentage	Group B	Percentage	Total
Romanian	16	76.19	31	68.89	47
Aromanian	3	14.29	7	15.56	10
Muslim	2	9.52	7	15.56	9
Total	21	100	45	100	66

Among the seronegative arthritis patients (group A), 16 patients (76.19%) are Romanian, 3 (14.29%) are Aromanians and only 2 patients (9.52%) are Muslims.

Social characteristics - distribution by smoker status:

In this clinical study, which included 66 patients with rheumatoid arthritis, it is noted that more than half of patients are no smokers (at the time of evaluation and history).

Table 22. Distribution of seropositive and seronegative RA patients according to smoking status.

Sex	Group A	Percentage	Group B	Percentage	Total
Smoker	10	47.62	22	48.89	32
Non smoker	11	52.38	23	51.11	34
Total	21	100	45	100	66

It was noted that less than half of the patients in each group are smokers (48.89% of seropositive RA patients and 47.62% of seronegative RA patients respectively), the frequency being slightly higher among smoking patients.

Social characteristics - distribution according to the educational level:

Regarding the educational level, it is observed that most patients have an average level of education (75.76%), higher education being part of the education of only 9.09% of the total number of patients included in the study. A number of 10 patients (15.15%) graduated only from the primary school.

Table 23. Distribution of seropositive and seronegative RA patients according to the educational level.

Age	Group A	Percentage	Group B	Percentage	Total
Higher education	1	4.76	5	11.11	6
Secondary school	14	66.67	36	80.00	50
Primary school	6	28.57	4	8.89	10
Total	21	100	45	100	66

There are differences between the two groups: seronegative arthritis patients (group A) have a lower level of education (secondary and higher education) than the seropositive patients (group B) (66.67% versus 80% and 4.76% versus 11.11%).

Studying the specialty literature, I have noticed in the study of Herman L. and his collaborators (1998) that RA diagnosed patients have a good compliance to DMARD treatment, regardless of their education level; the compliance in terms of preventive or pharmacological therapies is greater in patients with higher education.

Onset related features - association of the onset rheumatoid syndrome:

The rheumatoid syndrome defines, from the clinical point of view, the impaired polyarticular, symmetrical onset, which may be associated with the presence of rheumatoid factor. The first joints involved in the inflammatory process are the MCF, IFP and radiocarpal joint.

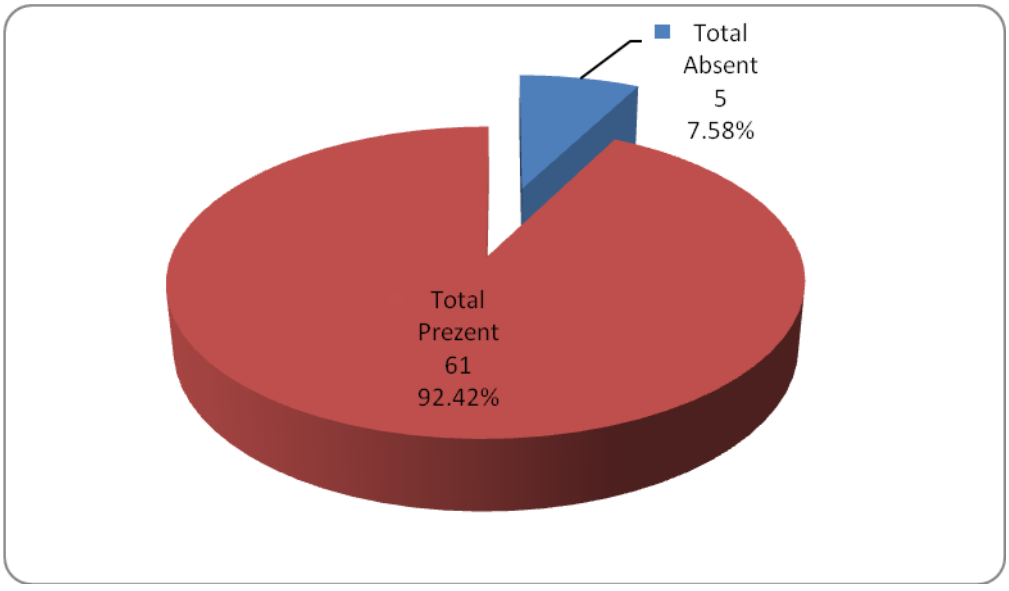

Chart 15. Distribution of RA patients according to the association of the onset rheumatoid syndrome

According to medical anamnesis, it appears that a significant percentage of patients in my study suffered from the rheumatoid syndrome at the disease onset (92.42% versus 7.58%)

Table 24. Distribution of seropositive and seronegative RA patients according to the association of the onset rheumatoid syndrome

Onset rheumatoid syndrome	Group A	Percentage	Group B	Percentage	Total
Absent	4	19.05	1	2.22	5
Present	17	80.95	44	97.78	61
Total	21	100	45	100	66

There were significant differences between the two groups regarding the onset rheumatoid syndrome association; thus, this form is to be met for 97.78% of seropositive RA patients, compared to 80.95% seronegative patients. The simultaneous onset impaired frequency of IFP and MCF joints is 88.89% (n = 40) of seropositive forms of disease which have associated a rheumatoid syndrome and only 38.09% (n = 8) of seronegative patients with this form of RA onset.

Onset related features – onset systemic manifestations association:

By means of "systemic manifestations" we refer to generalized fatigue, malaise, anorexia, fatigue, low grade fever, weight loss.

Only 25.76% of the 66 RA patients presented onset systemic manifestations; the information about the presence or absence of these manifestations were anamnestic obtained or by consulting the medical records of the patients.

Table 25. Distribution of seropositive and seronegative RA patients according to onset systemic manifestation association.

Onset systemic manifestation	Group A	Percentage	Group B	Percentage	Total
Absent	18	85.71	31	68.89	49
Present	3	14.29	14	31.11	17
Total	21	100	45	100	66

While analyzing the groups, statistically significant differences in terms of systemic manifestations occur at the onset of rheumatoid arthritis, which are present in 14.29% of disease seronegative forms (group A) and in 31.11% of disease seropositive forms (group B). Thus, based on these frequencies obtained in the present study, we can conclude that compared to the seronegative form of the disease, the seropositive rheumatoid arthritis has a more aggressive onset, which may be associated with constitutional symptoms.

Association of cardiovascular comorbidities in patients with rheumatoid arthritis:

It is known that rheumatoid arthritis is associated with an increased risk of cardiovascular events such as myocardial infarction or stroke.

In this study the following conditions were considered cardiovascular comorbidities: hypertension, ischemic heart disease, history of myocardial infarction and dyslipidemia. Their association with rheumatoid arthritis was recorded in 42.42% of patients included in the study, the percentage being majoritarian (57.58%) for those without a history of cardiovascular pathology.

Table 26. Distribution of seropositive and seronegative RA patients according to the association of cardiovascular comorbidities.

Cardiovascular comorbidities	Group A	Percentage	Group B	Percentage	Total
Absent	11	52.38	27	60.00	38
Present	10	47.62	18	40.00	28
Total	21	100	45	100	66

There were statistically significant differences between the two groups of patients, their presence being estimated at 40% in seropositive forms (group B) and 47.62% (group A) seronegative forms of disease.

Family history of inflammatory rheumatic diseases:

We found out that only 3 (4.55%) known RA patients had family history of inflammatory rheumatic diseases, out of which a number of 2 patients (one in group A and one in group B) had RA history and only one patient in group B had a history of ankylosing spondylitis.

Table 27. Distribution of seropositive and seronegative RA patients according to family history of inflammatory rheumatic diseases.

HC history inflammatory rheumatic diseases	Group A	Percentage	Group B	Percentage	Total
Absent	20	95.24	43	95.56	63
Present	1	4.76	2	4.44	3
Total	21	100	45	100	66

The genetic predisposition, assessed by family aggregation of the inflammatory rheumatic diseases, was found to be approximately equal between the two groups (4.44% in the seropositive group and 4.76% in the negative group).

Unlike the results obtained in this study, data from the specialty literature showed that constituted (defined) RA occurs more often in relatives of patients with seropositive form of the disease, unlike seronegative arthritis which appears not to have roots within the family. Equivalent data was obtained in twin studies that had similar joint damage only in form of seropositive disease.

Distribution depending on the age of the disease:

In this study patients with a disease duration of at least 2 years (established RA) were included, knowing the fact that within most patients osteoeroziv imaging changes as well as clinically evident joint deformities occur after at least two years of active disease. We also know that over 50% of patients stop working in the first 5 years of disease.

Therefore we considered it appropriate to analyse groups according to the duration of disease, and we took into account a disease duration older than 5 years.

Table 28. Distribution of seropositive and seronegative RA patients according to the duration of disease.

Dd ≥ 5 ani	Group A	Percentage	Group B	Percentage	Total
Absent	6	28.57	5	11.11	11
Present	15	71.43	40	88.89	55
Total	21	100	45	100	66

It was found that most RA patients, eligible for this study, present a duration of illness of at least five years, with a lower frequency in the seronegative patients group (71.43% versus 88.89%).

It is noted the fact that 6 patients (28.57%) of group A and 5 patients (11.11%) of group B present a duration of illness (RA) between 2 and 5 years.

Clinical evaluation of patients

The results of clinical evaluation of the 66 patients with established RA were comparative analysed among the two groups (seropositive and seronegative RA). No statistically significant differences, in terms of clinical examination at the time of evaluation, are stated; we refer to the average number of tender and swollen joints, DAS28 score (ESR / CRP), patient global assessment (VAS), as well as to the CDAI average value and to the Lee functional index.

Table 29. Characteristics of seronegative RA patients compared to RA seropositive ones.

Variables	Group A				Group B			
	Average	Standard Deviation	Minimum Value	Maximum Value	Average	Standard Deviation	Minimum Value	Maximum Value
DAS28 (ESR)	4.37	1.50	1.89	6.91	4.32	1.62	2.02	7.40
DaS28 (CRP)	3.74	1.55	1.48	6.72	3.68	1.57	1.31	6.75
No. of tender joints	7.62	8.21	0	26	7.89	8.90	0	28
No. of swollen joints	1.90	3.79	0	14	1.60	2.96	0	14
VAS	47.14	25.50	10	90	42.89	25.19	10	90
CDAI	18.95	14.48	2	46	18.09	14.67	2	50
SDAI	27.03	18.21	5.2	70.5	33.74	35.81	3.6	197
HAQ	2.82	1.47	1.1	7.1	2.66	1.46	1.05	8.12
Lee	16.10	9.60	4	33	17.27	8.57	2	34
Rheumatoid factor	7.73	1.55	5.6	12	132.58	299.96	6	1536
anti-CCP antibodies	1.81	0.75	1	4	645.77	1615.77	1.7	6577

Table 30. Distribution of seropositive and seronegative RA patients according to joint damage.

≥5 swollen joints in hands*	**Group A**	**Percentage**	**Group B**	**Percentage**	**Total**
Absent	16	76.19	30	66.67	46
Present	5	23.81	15	33.33	20
Total	21	100	45	100	66

* The metacarpophalangeal and proximal interphalangeal joints, that were swollen when assessing, were considered.

Differences were observed in the number of swollen joints at the time of evaluation; thus 33.33% of RA patients, with seropositive form, presented when assessing a form of clinically active disease with at least 5 swollen joints at the level of hands, compared to 23.81% of the seronegative patients.

We found a higher frequency of patients with seronegative arthritis who do not have swollen joints at the level of their hands or have less than 5 synovitis in MCF and IFP (76.19% versus 66.67%).

Complications of the underlying disease – association of joint deformities

Comparing the frequency of joint deformities of the hands among the two groups of patients included in the study (seropositive and seronegative RA), we found their superiority (in all their forms) among patients with seropositive arthritis. Most commonly they occur in combined version.

There were no significant differences regarding the proportion of patients who had “swan neck” or “buttonhole” deformities, ulnar deviation that cannot be corrected at the dominant or non-dominant hand. It seems that the middle and index finger of the dominant hand present more severe radiological changes. The functional deficit was also more severe at the dominant hand.

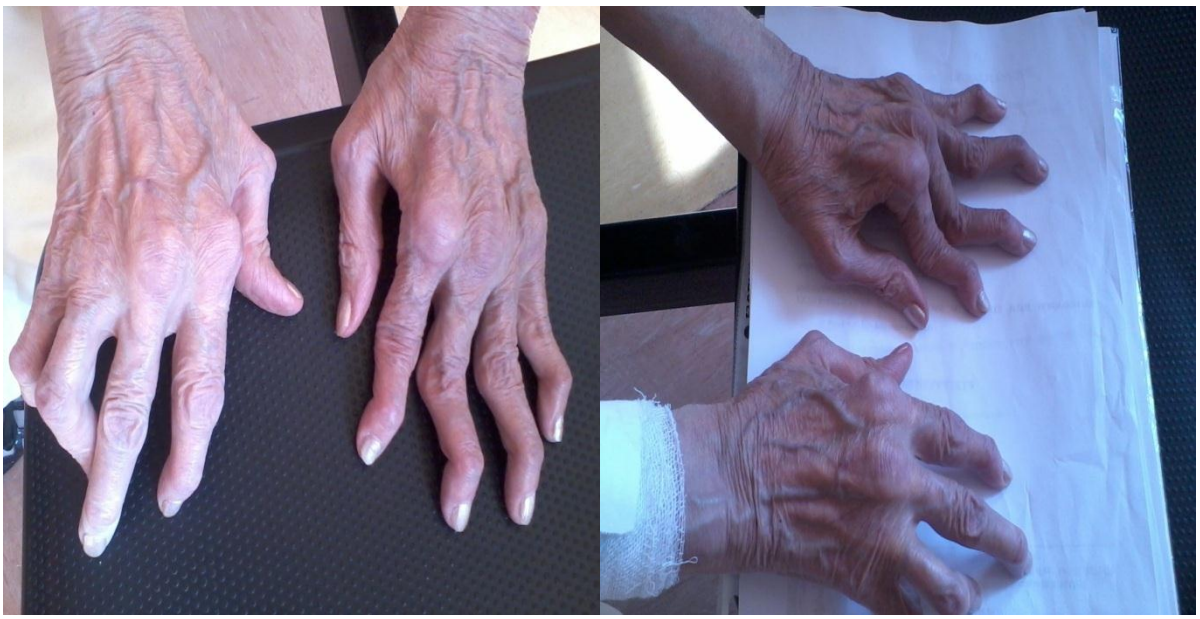

Fig 16. The hands of a 70-year-old female patient, diagnosed with seropositive RA (RF, anti-CCP antibodies) with a duration of illness of 20 years; the following is observed-clinical aspects: “swan neck” fingers, the left hand fingers II, III, IV, V, “buttonhole” fingers from the right hand (IV, V), “Z thumb” more accentuated on the right hand, radial carpal and ulnar deviation of the bilateral fingers, the interosseous muscle atrophy, metacarpalphalangeal and radiocarpal ankylosis.

Complications of the underlying disease – associating the clinical evident articular ankylosis.

Severe ankylosis of the hands’ joints, clinical evident (stage IV according to Steinbrocker’s functional staging – lost functional capacity), represent complications that can occur during the development of rheumatoid arthritis.

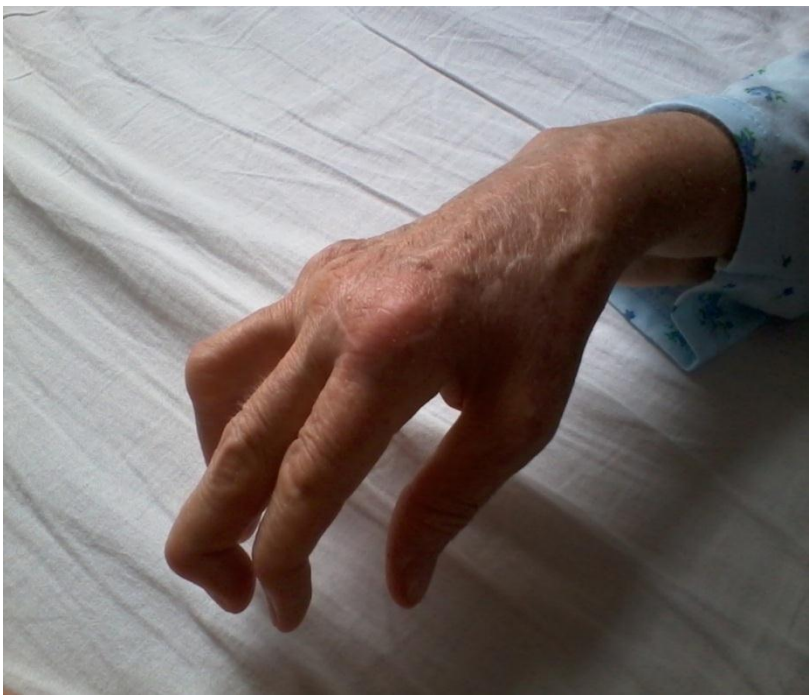

Fig.17 – The right hand of a 73-year-old female patient, diagnosed with seropositive RA for 14 years; the severe existent ankyloses are to be observed: ankylosis in flexion at the IFD level, fingers II, III and IFP, finger IV; complete ankylosis of the MCF and RC.

Table 31. Distribution of seropositive and seronegative RA patients according to the association of the clinical evident articular ankyloses

Severe joint ankyloses located at the hands (functional block)	Group A	Percentage	Group B	Percentage	Total
Absent	17	80.95	27	60.00	44
Present	4	19.05	18	40.00	22
Total	21	100	45	100	66

There were statistically significant differences between the two groups in terms of progress towards ankylosis, these having a significantly higher frequency among the RA seropositive patients. For example, 40% of the seropositive RA patients have severe ankyloses compared to only 19.05% of patients with seronegative form of the disease.

Imaging assessment of patients

Tin order to imaging assess small joints of the hands, affected during RA, radiographs of hands were made or we used those existent within the medical documentation of patients (for all 66 patients); there was also a musculoskeletal ultrasound performed in the case of 27 patients (20 seropositive and 7 seronegative)

and the confirmation by magnetic resonance of articular and periarticular pathology was followed in the case of 12 patients (3 seropositive and 9 seronegative).

Complications of the underlying disease – radiological changes:

According to Steinbrocker's radiological staging, during the 1st and 2nd stages, the hand radiographs belonging to patients with clinical diagnosis of rheumatoid arthritis can present no changes or periarticular demineralization and/or joint space narrowing can occur.

Table 32. Distribution of seropositive and seronegative RA patients according to the radiographic changes.

Radiography	Group A	Percentage	Group B	Percentage	Total
no changes	2	9.52	0	0.00	2
demineralization	4	19.05	8	17.78	12
narrowing	0	0.00	2	4.44	2
demineralization and narrowing	15	71.43	34	75.56	49
Total	21	100.00	44	97.78	65

In the case of the 66 RA patients included in this study, there was a frequency of only 3.08% (n = 2) of patients whose radiographs of hands do not present changes, both patients being part of the group A, meaning that they are patients with definite diagnosis of seronegative RA. Most polyarthritis patients (75.38%) radiologically associate periarticular demineralization with joint space narrowing. No statistically significant differences between the two groups in terms of frequency of associated radiographic changes (group A versus 71.43% 75.56% group B) are to be observed.

Table 33. Distribution of seropositive and seronegative RA patients according to radiographic changes.

Radiography	**Group A**	**Percentage**	**Group B**	**Percentage**	**Total**
geodes	9	42.86	24	53.33	33
erosions	10	47.62	30	66.67	40
ankylosis and subluxations	5	23.81	13	28.89	18

We have observed statistically significant results in group B, which includes seropositive RA patients; thus, the occurrence rate of subchondral geodes and bone erosions is significantly higher in group B (53.33% versus 42.86% and 66.67% versus 47.62% respectively), and related to the existence of ankyloses and subluxations, the share is also lower within the group of seronegative patients.

I found out that in my study, the radiological changes at the hands' level have a lower severity degree within the patients diagnosed with established (defined) rheumatoid arthritis.

A meta-analysis of the studies conducted so far revealed two conclusions:

- the presence of radiological lesions, osteoeroziv type and of joint damages at the level of the hands is equal between the two types of RA (seropositive and seronegative);
- a greater joint fusion grade occurs in seronegative patients.

More severe radiological changes at the level of the dominant hand were reported by Mattingly (in a study of 30 RP patients) ulterior confirmed by Owsianik and Mody.

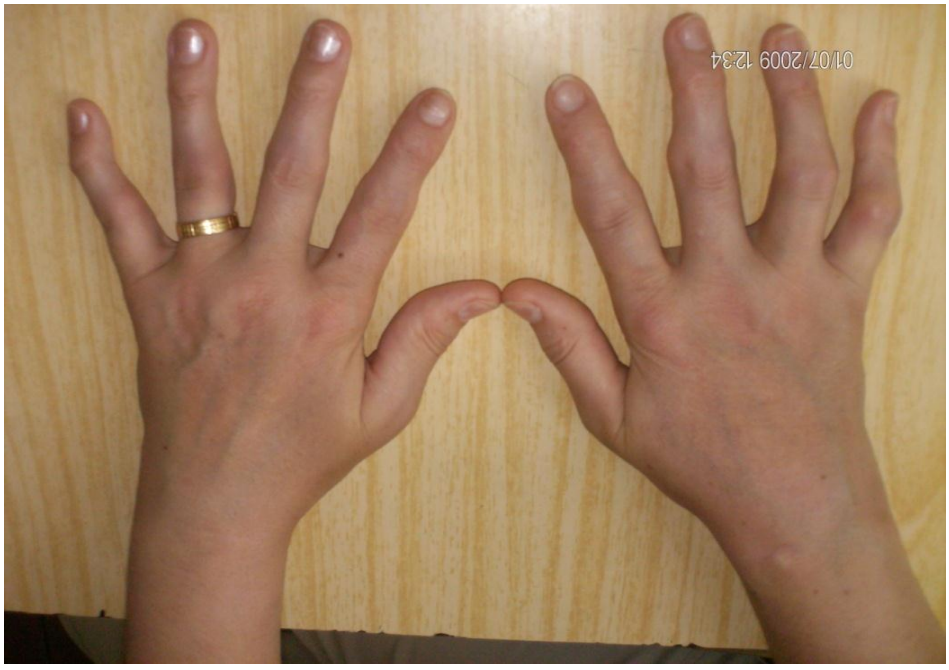

Fig. 18 – Seropositive RA female patient (positive RF, anti-CCP negative antibody) 3rd phase, with a disease duration of 24 years; to be observed: "Z thumb", clinical aspect of "spindly fingers" with synovitis in MCF and IFP, IFP rheumatoid nodules II, III left hand, "buttonhole fingers" IV, V right hand, IFD ankylosis in flexion III right hand, left IFD V hand.

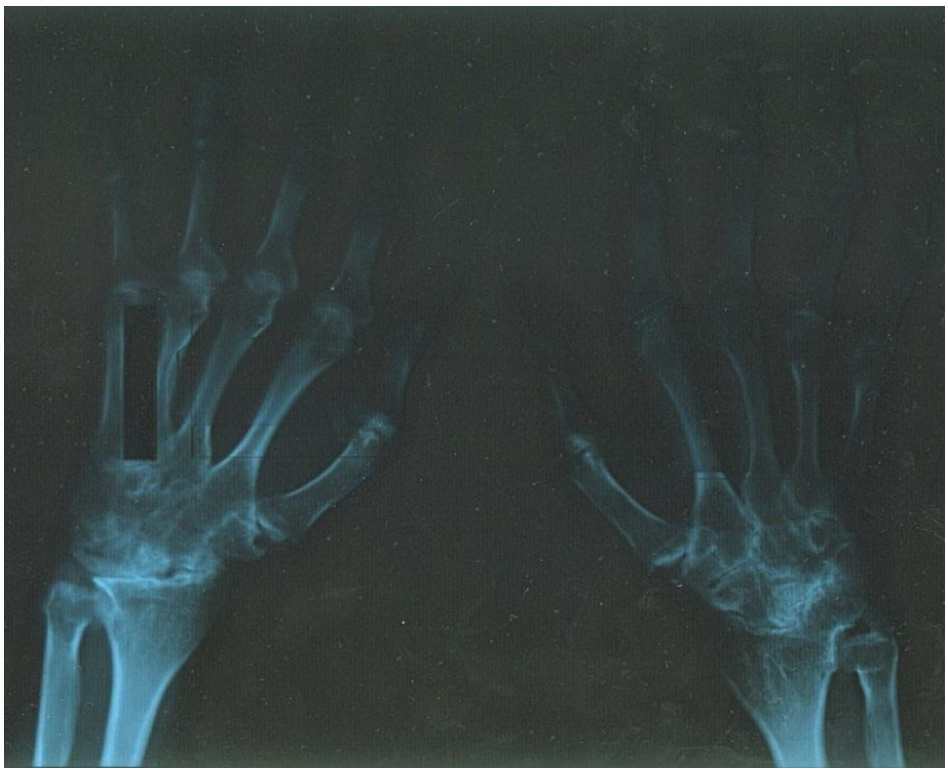

Fig. 19 – The corresponding radiography demonstrates: osteoerozive destructive lesions in the carpus, subchondral carpal microgeodes, marginal erosions at the MCF and IFP level, joint space narrowing, periarticular demineralization.

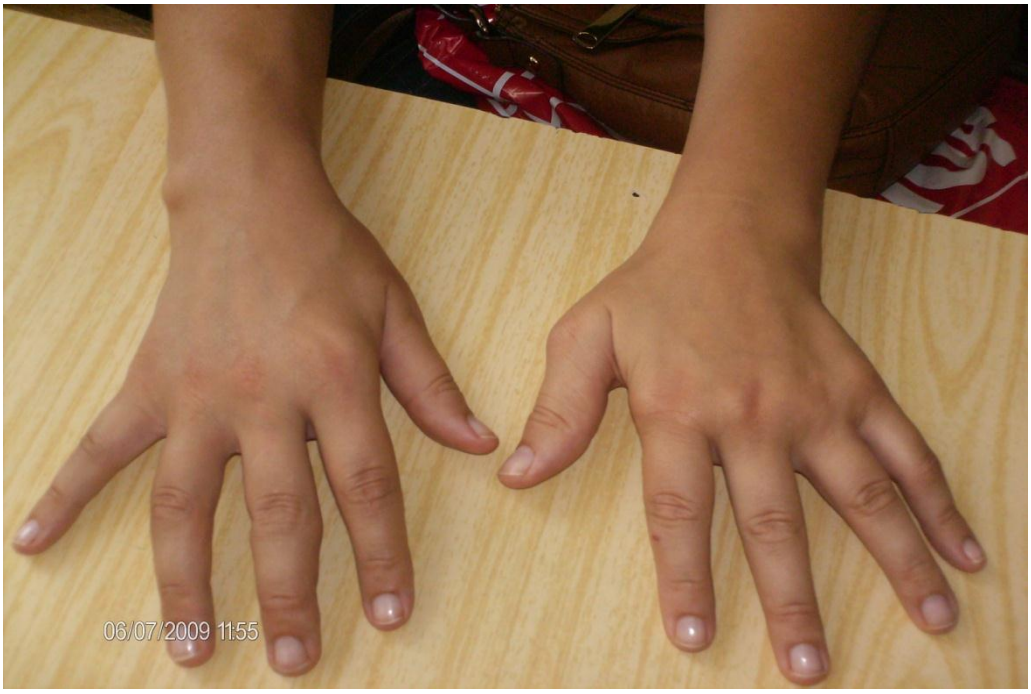

Fig. 20 – Seropositive RA female patient (negative RFanti-CCP positive antibodies) 4th phase, disease duration of 10 years; it presents: IFP synovitis, IFP semiankylosis in flexion, slight radial carpal and ulnar deviation of the fingers.

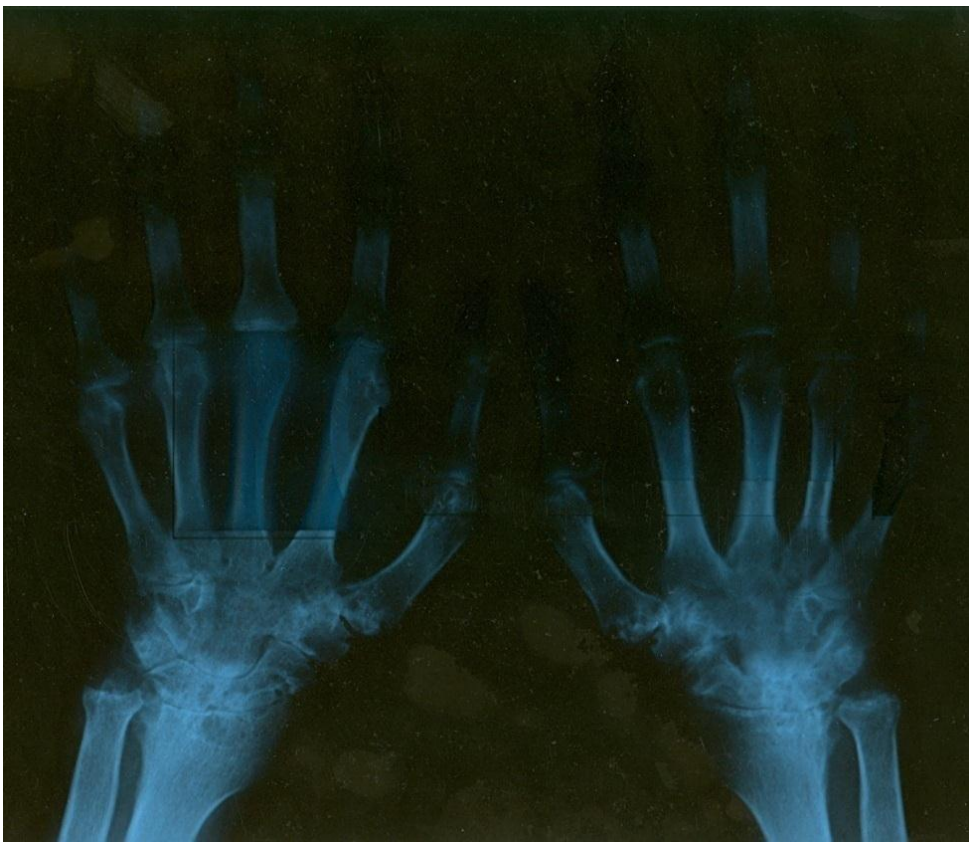

Fig. 21 – The corresponding radiograph demonstrates: osteoerozive carpal injuries, subchondral geodes and periarticular erosions at the level of MCF and VET joints intercarpal joints space narrowing, MCF and IF.

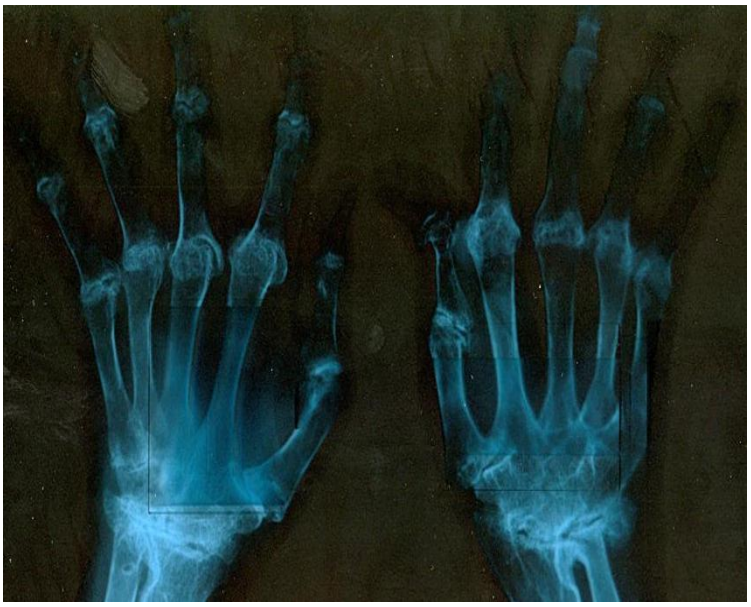

Fig. 22 – Carpus and metacarpus bone erosions; displacement of the sesamoid bones within the thumb on both hands.

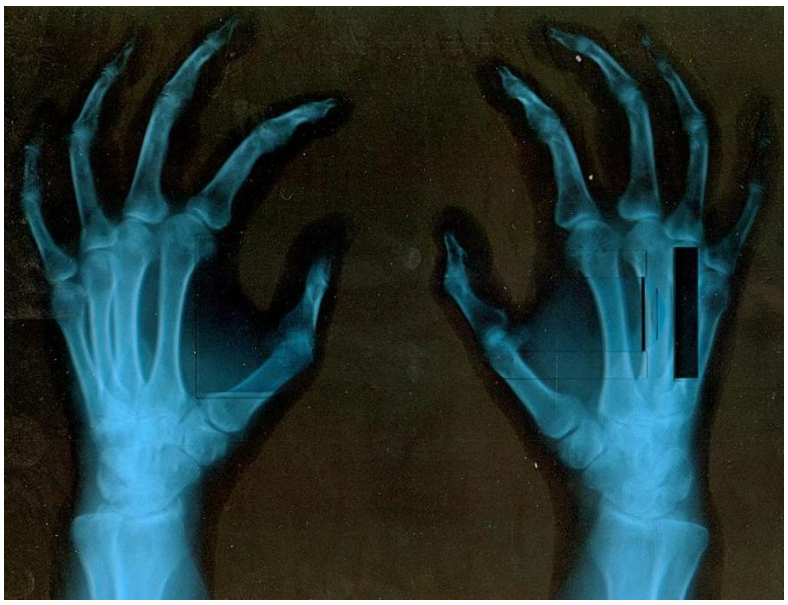

Fig. 23 – Carpal and metacarpal bone erosions at the level of both hands; displacement of the sesamoid bones within the right thumb.

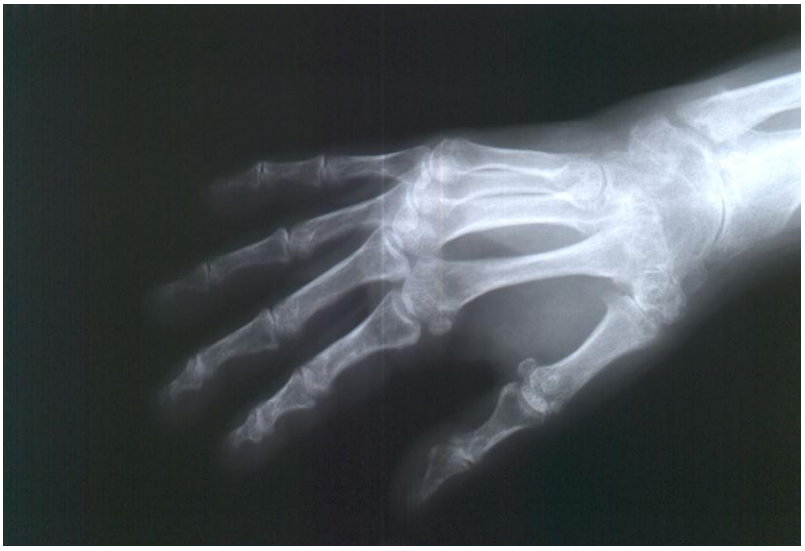

Fig. 24 – RA seronegative female patients (RF, anti-CCP antibodies) 4th phase, with a disease duration of 39 years; the followings are observed: diffuse bone demineralization, sharp narrowing and synostosis in the intercarpal spaces forming a “block bone”, semiankylosis in flexion at the MCF level, osteolysis areas at the carpus level, MC, average finger phalanx III, multiple subchondral geodes and periarticular erosions at the level of carpal bones, MC and phalanges.

Table 34. Predictive factors for the radiological occurrence of erosions.

Variables	Risk (OR)
Male	1.1739
Positive Ac anti-CCP	1.8571
Family aggregation of inflammatory rheumatic diseases	0.3077
Disease duration	0.8541
Extra-articular manifestations	2.1667
Rheumatoid syndrome onset	1.0278
systemic manifestations onset	1.2644

The most polyarthritis patients are in the 2nd or 3rd phase disease (33.33% and 40.91%); only two patients are diagnosed with stable seronegative RA, 1st phase.

The 2nd disease stage is more frequent in group A (seronegative RA), 38.10% compared to 31.11% of group B.

Group B, which falls as seropositive arthritis, presents a more advanced radiological destruction compared to group A, the proof being a bigger share of 3rd and 4th stages. Thus, 44.44% of the patients belonging to group B are in the 3rd stage compared to 33.33% of the patients belonging to group A, while 24.44% and 19.05% respectively are in the 4th stage disease.

Table 35. Distribution of RA seropositive and seronegative patients according to the radiological stage.

Steinbrocker's radiological staging	Group A	Percentage	Group B	Percentage	Total
1st stage	2	9.52	0	0.00	2
2nd stage	8	38.10	14	31.11	22
3rd stage	7	33.33	20	44.44	27
4th stage	4	19.05	11	24.44	15
Total	21	100.00	45	100.00	66

Related to this risk, it seems that 24.24% of the patients studied have a limited functional capacity and only 10.61% have a lost functional capacity.

Table 36. Distribution of RA seropositive and seronegative patients according to Steinbrocker's functional classification.

Steinbrocker's functional classification	Group A	Percentage	Group B	Percentage	Total
normal (1st class)	1	4.76	1	2.22	2
pain while moving (2nd class)	14	66.67	27	60.00	41
limited functional capacity (3rd class)	5	23.81	11	24.44	16
lost functional capacity (4th class)	1	4.76	6	13.33	7
Total	21	100.00	45	100.00	66

Analyzing groups, we found statistically significant differences related to the functionality degree; one can observe in group B (seropositive RA) patients with high frequency of lost functional capacity (4th class) as well as those with limited functional capacity (3rd class).

Group A (seronegative RA) discloses a higher proportion of patients belonging to 1st and 2nd functional classes (4.76% versus 2.22% and 66.67% respectively versus 60%).

Complications of the underlying disease - carpal tunnel syndrome

The carpal tunnel syndrome is the most common peripheral neuropathy caused by compression of the median nerve at the carpal tunnel passage.

It is produced by the radiocarpal synovitis and the lack of elasticity of the transverse carpal ligament, that presses the median nerve.

This type of peripheral neurological damage, expressed as carpal tunnel syndrome was met at 18.18% of the patients in our study.

Table 37. Distribution of RA seropositive and seronegative patients according to the carpal tunnel syndrome.

Carpal tunnel syndrome	Group A	Percentage	Group B	Percentage	Total
present	3	14.29	9	20.00	12
absent	18	85.71	36	80.00	54
Total	21	100	45	100	66

According to DE Hastings's study (1975) it seems that the carpal tunnel syndrome is found in 1-5% of patients with rheumatoid arthritis.

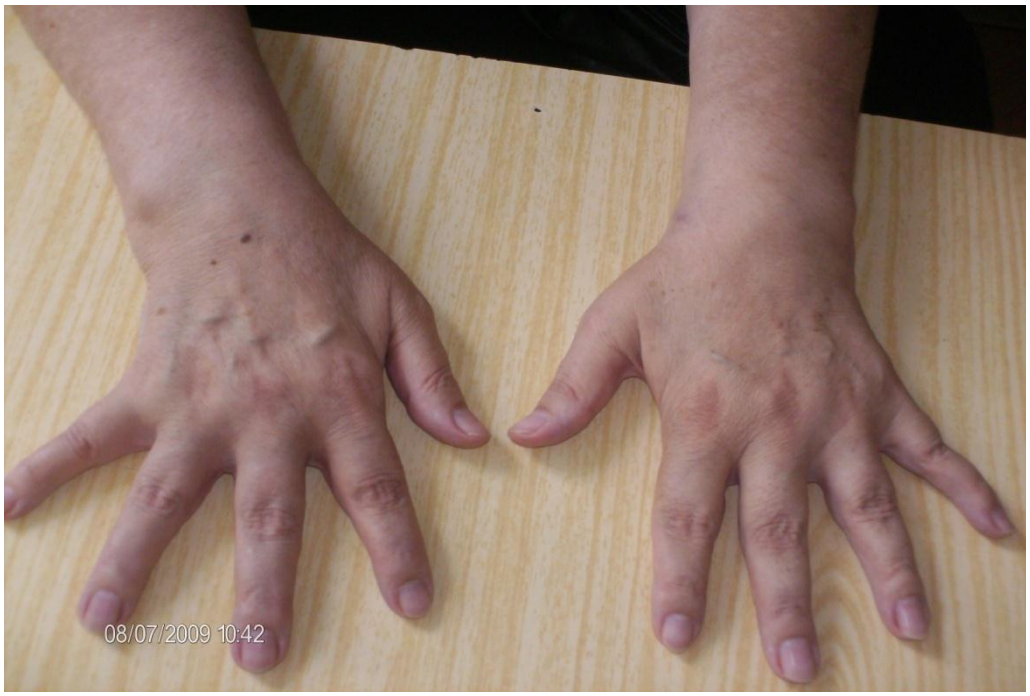

Fig 25 – RA seropositive female patient (positive RF, negative anti-CCP antibodies) 3rd stage, with a duration of illness of 14 years; it is observed: RC persistent synovitis, MCF, IFP. The carpal tunnel syndrome is also present.

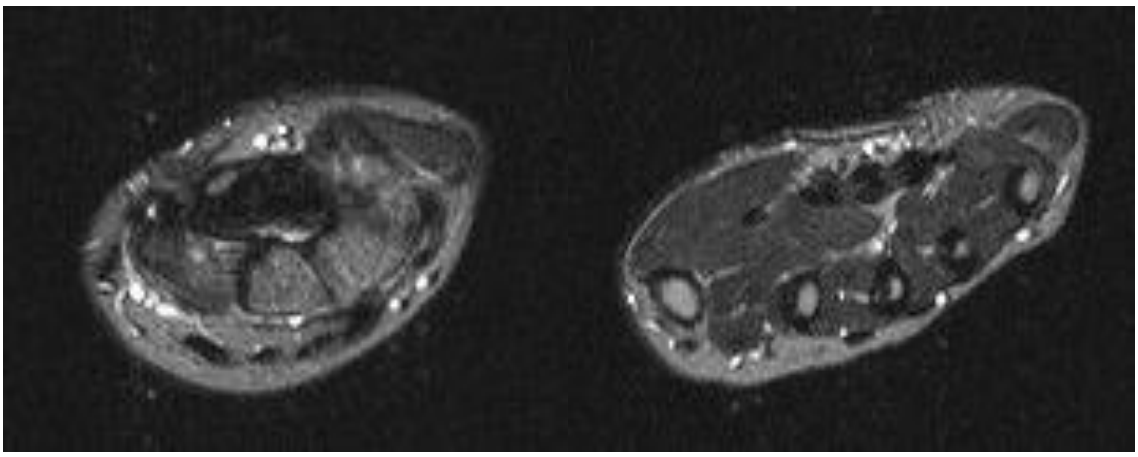

Fig. 26 – RMN images. Carpal tunnel syndrome for the female patient from above. T2 fat sat image. Diffusely infiltrated fluid is observed in the superficial soft tissues and fluid accumulation within the metacarpocarpal synovial joints.

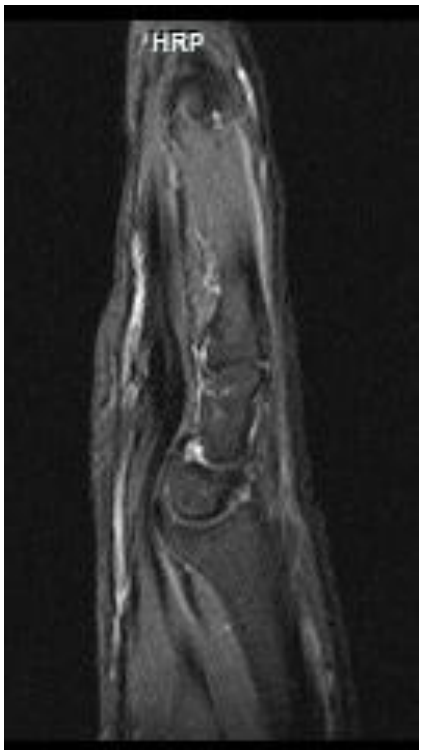

Fig. 27 – Carpal tunnel syndrome. T2 fat sat image. The signal stands fluid infiltration of synovial sheaths of tendons crossing the carpal tunnel is to be noticed, without any alteration of the tendon signal; fluid signal diffusely infiltrated within the soft tissues superficial, to the interface with the palmar fascia and small fluid accumulation in the intercarpal synovial joint.

Sonographic features:

Considering the ultrasound aspect, there are differences between groups; a slightly higher frequency of tenosynovitis, synovitis and bone erosions at the hands

level is to be observed within RA seronegative patients. Joint effusion has a slightly higher frequency within seropositive patients (26.67% versus 23.81%).

These conflicting results between radiographic and ultrasonographic aspects, probably result from the selection of patients who have performed hand ultrasound, among those with inconclusive radiological results.

Table 38. Distribution of RA seropositive and seronegative patients according to the sonographic features

Ultrasound	Group A	Percentage	Group B	Percentage	Total
tenosynovitis	5	23.81	8	17.78	13
effusion	5	23.81	12	26.67	17
erosion	4	19.05	7	15.56	11
synovitis	1	4.76	2	4.44	3

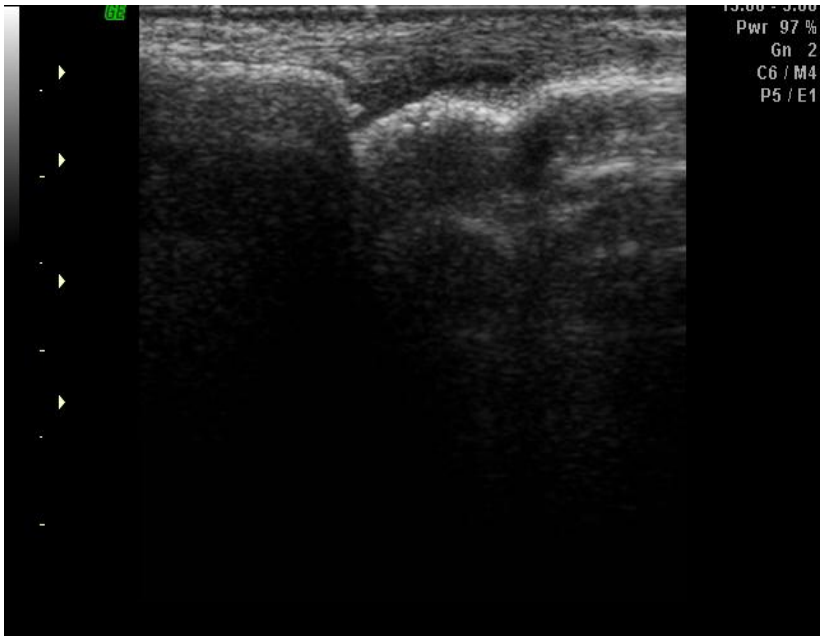

Fig. 30 – Musculoskeletal ultrasound; joint effusion is highlighted, without Doppler signal.

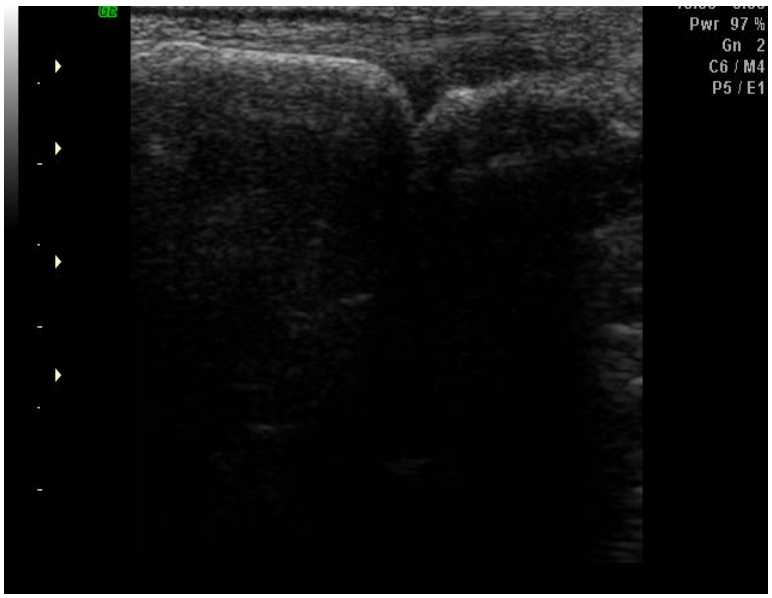

Fig. 31 – Musculoskeletal ultrasound; joint effusion is highlighted, without Doppler signal.

RMN changes within RA patients

Nuclear magnetic resonance examination of pathological aspects in the hands of 12 RA patients (9 patients with seronegative form of the disease) showed statistically significant differences between the two groups. Thus, synovitis and bone erosions were found only within seronegative patients, at the rate of 9.52% and 19.05% respectively, while tenosynovitis appears only at one seropositive patient; the results are probably explained by the way of selection of the patients who performed RMN.

Table 39. Distribution of RA seropositive and seronegative patients according to the RMN features.

RMN	Group A (N=9)	Percentage	Group B (N=3)	Percentage	Total
erosions	4	19.05	0	0.00	4
tenosynovitis	0	0.00	1	2.22	1
synovitis	2	9.52	0	0.00	2
tenosynovitis & synovitis	0	0.00	0	0.00	0
geodes	5	23.81	0	0	5

Therapeutic particularities:

The analysis of rheumatoid arthritis patients, divided into two groups seronegative RA patients (group A) and seropositive RA patients (group B) showed

some differences and similarities in terms of the response to DMARD treatment or biologic therapy.

Table 40. Distribution of RA seropositive and seronegative patients according to the therapeutic particularities.

	Group A	Percentage	Group B	Percentage	Total
no treatment	13	61.90	10	22.22	23
biological therapy	0	0.00	0	0.00	0
biological therapy and DMARD	1	4.76	9	20.00	10
combined therapy	4	19.05	18	40.00	22
triple therapy	3	14.29	8	17.78	11
Total	21	100.00	45	100.00	66

Table 41. Distribution of RA seropositive and seronegative patients according to the therapeutic particularities

DMARD	Group A	Percentage	Group B	Percentage	Total
current maximum doses	5	23.81	28	62.22	33
used in the past	16	76.19	44	97.78	60

Table 42. Distribution of RA seropositive and seronegative patients according to the therapeutic particularities.

AINS maximum dose	Group A	Percentage	Group B	Percentage	Total
present	2	9.52	15	33.33	17
occasional	19	90.48	30	66.67	49
Total	21	100	45	100	66

What one can notice in the two groups is that there is a significantly higher frequency among seronegative patients who did not require medical treatment when evaluating (61.90% versus 22.22%). There is a high frequency (20%) within the

seropositive patients treated with DMARD and biologic therapy, compared to the seronegative patients (4.76%).

There is also a statistically significant difference regarding the maximum dose needs of disease-modifying therapies (DMARD) and the need for anti-inflammatory drugs (AINS), the rates being significantly higher within patients with seropositive form of the disease (62.22% versus 23.81 % and 33.33% versus 9.52%).

Statistically significant differences were also noticed in the cases where combination therapy or triple therapy was used, higher frequencies within seropositive patients being recorded (40% versus 19.05% and 17.78% versus and 14.29% respectively).

Table 43. Distribution of RA seropositive and seronegative patients according to the therapeutic particularities.

Corticotherapy:

	Group A	Percentage	Group B	Percentage	Total
no corticotherapy	17	80.95	28	62.22	45
corticotherapy	4	19.05	17	37.78	21
Total	21	100	45	100	66

Regarding the corticotherapy, statistically significant differences between groups were observed; thus, when evaluating, 37.78% of RP seropositive patients were on corticotherapy as background medication, and only 19.05% of the seronegative patients were under cortisone treatment.

The activity degree of rheumatoid arthritis

Table 44. Distribution of RA seropositive and seronegative patients according to the occurrence of disease remission under treatment

	Group A	Percentage	Group B	Percentage	Total
without remission	15	71.43	34	75.56	49
remission at DMARD	6	28.57	8	17.78	14
remission at biological	0	0.00	3	6.67	3

therapy					
Total	21	100.00	45	100.00	66

Table 45. Distribution of RA seropositive and seronegative patients according to the degree of disease activity.

DAS28	Group A	A Percentage	Group B	B Percentage	Total
<2.6	5	23.81	10	22.22	15
2.6 -3.2	3	14.29	11	24.44	14
3.2-5.1	7	33.33	11	24.44	18
>5.1	6	28.57	13	28.89	19
Total	21	100.00	45	100.00	66

Complete remission was considered when the patient had at the time of the evaluation a disease activity score of 28 (DAS28 – Disease Activity Score 28) less than 2.6.

Regarding the remission under DMARD treatment (DAS28 < 2.6), it has been shown that this aspect is quite similar even as frequency in the two groups (22.22% versus 23.81%). The remission under biological therapy was noted within 3 seropositive RA patients, namely within 4.55% of the patients in the present study (n = 66).

CONCLUSIONS

The clinical course of rheumatoid arthritis is variable and it is difficult to determine its prognosis. Approximately one third of RA patients are seronegative for both serologic markers, the rheumatoid factor (RF) and the antibodies against cyclic citrulline peptide (anti-CCP antibodies).

The main objective of the present study has been to draw up a scientific comparative analysis in terms of morphological, clinical and imaging of small joints of the hands, within seropositive and seronegative rheumatoid arthritis.

Personal findings are compared to available data from the specialty literature, some of which being less reported in the literature that I had the opportunity to consult.

Regarding the particularities of the group of patients with established (defined) rheumatoid arthritis that were included in this study, we can make the following observations:

• in the study group, in both forms of rheumatoid arthritis, the female patients dominated (89.39%), the predominant age group being between 51-85 years. In addition, in both sexes, in the studied groups, the majority were ethnic Romanian patients from the urban area.

• unlike the data from the specialty literature, which proves that smoking is a risk factor certainly involved in the etiology of rheumatoid arthritis, according to the results obtained in our study, the frequency is slightly higher among no smoking patients.

• genetic predisposition, evaluated by means of family aggregation of inflammatory rheumatic diseases was found to be approximately equal between the two groups (4.44% in the seropositive group and 4.76% in the negative group).

• 97.78% of seropositive RA patients associate the onset rheumatoid syndrome, compared to 80.95% of the seronegative patients.

• MCF and IFP joints are simultaneously affected at the beginning of the disease at the value of 88.89% (n = 40) of the seropositive disease forms which have associated the rheumatoid syndrome and only at 38.09% (n = 8) of the seronegative patients.

• 33.33% of RA patients, seropositive form, presented when evaluating a form of clinically active disease with at least 5 swollen joints in hands, compared to 23.81% of the seronegative patients.

• we obtained similar results to those given in the specialty literature regarding the superiority of joint deformities of the hands within patients with seropositive form of the disease.

• the carpal tunnel syndrome was met within 18.18% of the patients in our study, namely at a significantly higher percentage compared to the data specified in the specialty literature.

• 40% of seropositive RA patients have severe ankylosis, compared to only 19.05% of patients with seronegative form of disease; therefore, the functional deficiency is more severe within seropositive disease forms.

• the rate of the subchondral geodes occurrence and of bone erosions is significantly higher within the group of seropositive patients (53.33% versus 42.86% and 66.67% versus 47.62%) and regarding the existence of ankylosis and subluxations, the grade is also lower within the group of seronegative patients.

• I have obtained conflicting results between radiological aspects, ultrasound and RMN probably resulted from the patients selection, among the patients with uncertain clinical changes.

• Concerning the requirements of maximum doses of disease-modifying therapies (DMARD) and the need for anti-inflammatory drugs (AINS), the frequencies are considerably higher within patients with seropositive form of the disease (62.22% versus 23.81% and 33.33% versus 9.52% respectively).

• Pain, stiffness and functional impotence are the main symptoms that characterize rheumatoid arthritis, forming major causes of temporary or even permanent employment incapacity, with significant personal and social costs and implications.

The anatomical study of the patients' hands presented with rheumatoid arthritis revealed significant results in terms of elements of this branch, such as the sesamoid bones visible on plain radiographs performed for both hands, but also on 2D and 3D reconstructions shown by a computed tomography.

The sesamoid bones of the hand show a great variability related to the number, location, shape and size, displaying particular characteristics from an individual to another. It is not compulsory the presence of one or more sesamoid bones, I being able to find their absence in 13.04% of the cases studied so far. I have also found a discrepancy between morphological characteristics of the sesamoid

bones beside the two parts of the body. The sesamoid bones serve for muscle insertions (thenar eminence muscles) and ligaments (ligaments of metacarpophalangeal or interphalangeal joint), also receiving tendinous expansions. Regardless of their number and location, the sesamoid bones are located only on the palm.

Medial and lateral collateral ligaments of the metacarpophalangeal joint of the thumb are placed on the medial or lateral tubercle of the metacarpal head, then they are displayed to fit on the first phalanx on the palmar ligament and sesamoid bones, so, the sesamoid bones serve as supporting ligament, thus increasing their resistance. That may explain the higher frequency of the absence of sesamoid bones on the left side, most people being right-handed. After Rouvière, their main roles are represented by the changing pressure, the friction reduction, and sometimes the direction change of the muscle pull. In accordance with Moore, the sesamoid bones protect the tendons from excessive friction and they frequently contribute to the change of the tendon insertion angle.

Reviewing the databases related to patients with seronegative RA forms, one can observe a lack of epidemiological data and the absence of studies on evolutionary features. It is discussed a lot about the cases of seronegative symmetrical polyarthritis which created problems related to the differential diagnosis and the extraarticular manifestations are rarely reported in clear cases of seronegative rheumatoid arthritis.

The clinical results achieved in this paper complement the data from the studies of renowned authors who have analysed the characteristic features of rheumatoid arthritis according to seropositivity.

My results confirm the very clear idea that the seronegative rheumatoid polyarthritis has a milder clinical course and it is a less destructive form of disease, the present study greatly contributing to this idea.

BIBLIOGRAFIE GENERALĂ

1. ALAN HAKIM, GAVIN CLUNIE, INAM HAQ; Oxford Handbook of Rheumatology, Second Edition 2008; 236, 240.
2. ALETAHA D, MACHOLD KP, NELL VP, SMOLEN JS. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology (Oxford) 2006; 45:1133.
3. ALETAHA D, NEOGI T, SILMAN AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-81.
4. ANDONOPOULUS AP, DROSOS AA, et al: Secondary Sjogren's syndrome in rheumatoid arthritis. J Rheumatol 14:1098, 1987.
5. ARNETT FC, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.
6. BACHMEYER C, CHAROUD A, MOUGEOT-MARTIN M. 2003. Clin Rheumatol; Rheumatoid nodules indicating seronegative rheumatoid arthritis in a patient with gout; 22:154-5.
7. BARKER JA, SEBES JI: Rheumatoid arthritis of the robust-reaction type. Arthritis Rheum 41:1131-1132, 1998.
8. BAUM J: Infection in rheumatoid arthritis. Arthritis Rheum 14:135-137, 1971.
9. BEAUTHIER J.P., LEFEVRE PH., - Traité d'Anatomie., de la théorie à la pratique palpatoire. Tome 2. Membre supérieure et ceinture scapulaire. Ed. De Boeck Université, Bruxelles, 1991, pag. 261.
10. BLAND JH, BROWN EW. Seronegative rheumatoid arthritis: clinical, radiological and biochemical differences. Ann Intern Med 1964; 60: 88-94.
11. BONAGURA VR, WEDGWOOD JF, et al. Seronegative rheumatoid arthritis, rheumatoid factor cross reactive idiotype expression, and hidden rheumatoid factors. Annals of the Rheumatic Diseases 1989; 48:488-495.
12. BONNEL F., CHEVREL J.P., OUTREQUIN G. – Anatomie Clinique. Les membres. Ed. Spriger-Verlag, Paris, 1991, pag. 217-285.

13. COLE BC, GRIFFITHS MM: Triggering and exacerbation of autoimmune arthritis by the Mycoplasma arthritidis superantigen MAM. Arthritis Rheum 36:994,1993
14. COMBE B. Progression in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2009; 23: 59-69.
15. CRONIN ME,. Musculoskeletal manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 1988, 14:99.
16. CUSHNAGHAN J, MCDOWELL J. Rheumatological conditions. Drug Therapy in Rheumatology Nursing. Second Edition, 2007.
17. D.P.M.SYMMONS: Looking back: rheumatoid arthritis-aetiology, occurrence and mortality. Rheumatology 2005;44(Suppl. 4):iv14–iv172005
18. DIXON A ST J. 'Rheumatoid arthritis' with negative serological reaction. Ann Rheum Dis 1960; 19: 209-17.
19. DORAN MF, POND GR, CROWSON CS, et al. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 46:625-631, 2002.
20. FELSON DT, ANDERSON JJ, BOERS M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993; 36:729-40.
21. FINCKH A, DEHLER S, et al. Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis 2007, 66; 1066-1071
22. FIRESTEIN GS, ZVAIFLER NJ: How important are T cells in chronic rheumatoid synovitis? T cell-independent mechanisms from beginning to end. Arthritis Rheum 46:298, 2002.
23. FLEMING A, CROWN JM, CORBETT M: Early rheumatoid disease,I: Onset.II. Paterns of joint involvement. Ann Rheum Dis 35:357-360, 1976.
24. FORSLIND K, HAFSTROM I, et al. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007; 66:46-52.
25. FRANCES FISCHBACH. Immunodiagnostics studies. Lippincott Williams and Wilkins, USA, 7 Ed, 2004, 604-605.
26. FRANCESCO DATI, ERWIN METZMANN. Autoimmune Disease. In Proteins Laboratory Testing and Clinical Use, Media Print Taunusdruck GmbH, Frankfurt am Main; 2005, 214, 225-226.

27. FRIES JF, SPITZ P, KRAINES RG, HOLMAN HR. Measurement of patient outcomes in arthritis. Arthritis and Rheumatism, 23. 1980, pp 137-145.
28. FUCHS HA, et al. Evidence of significant radiographic damage in rheumatoid arthritis with in the first 2 years of disease. J Rheumatol 1989. 16:585-591.
29. GABRIEL SE. Heart disease and rheumatoid arthritis: understanding the risks. Ann Rheum Dis 2010; 69. 61-64.
30. GARY S FIRESTEIN, RALPH C. BUDD, EDWARD D. HARRIS, Jr, et al: Kelleys. Textbook of Rheumatology, Eighth Edition, 2009; 1035
31. GER JM PRUJIN, ERIK R VOSSENAAR, et al: Anti-CCP antibody detection facilates early diagnosis and prognosis of rheumatoid arthritis. In Current Rheumatology Reviews. 1:1-7.2005. Ref Type:Journal (Full)
32. GHIDUL SERVICIILOR MEDICALE AL LABORATOARELOR SYNEVO, ediţia 2007-2008.
33. GLADER B. Anemia: General considerations. In Wintrobe's Clinical Hematology, Philadelphia ed. 1996, 293-316.
34. GORDON DA, et al. Rheumatoid arthritis-contemporary patient management series. 2d ed. Medical Examination Publishing, New York. 1985.
35. GOUGH J, RIVERS D, SEAL RME. Pathological studies of modified pneumoconiosis in coal-miners with RA (Caplan's syndrome). Thorax. 1955: 10:9.
36. GRAHAM TB, LAOR T, Dardzinski BJ; Quantitative magnetic resonance imaging of the hands and wrists of children with JIA; J Rheumatol 2005; 32: 1811-20;
37. GREEN MJ, DEODHAR AA. Bone changes in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2001. 15:105-23.
38. GREGERSEN PK, SILVER J, WINCHESTER RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30:1205-13.
39. GUILPAIN P, KETTANEH A, CHARMOUARD JM et al. 2003. Rev med Interne ; Compression of the spinal cord revealing a seronegative rheumatoid arthritis ; 24 : 59-62
40. GYLYS-MORIN VM, GRAHAM BT,BLEBEA JS şi colaboratorii; Knee in early juvenile rheumatoid arthritis: MR imaging findings; Radiology 2001; 220: 696-706;

41. H. BOLOSIU, R. IONESCU, R CHIRIEAC, L. GEORGESCU, S. REDNIC, M. SUTA, C. CODREANU: Ghidul de tratament al poliartritei reumatoide, Revista Romana de Reumatologie, Vol.XX, Nr 1, 2011.
42. HALLA JT, SCHROHENLOHER RE, KOOPMAN WJ: Local immune responses in certain extra-articular manifestations of rheumatoid arthritis. Ann Rheum Dis 51:698-701,1992.
43. HARRIS ED JR, SCHUR PH. Overview of the management of rheumatoid arthritis. www.uptodate.com
44. HASTINGS DE, EVANS JA. Rheumatoid wrist deformities and their relation to ulna drift. J Bone Joint Surg 1975, 57A:930.
45. HENCH PS, ROSENBERG EF: Palindromic rheumatism: New oft-recurring disease of joints (arthritis, periarthritis, para-arthritis) apparently producing no articular residues-report of 34 cases. Proc Mayo Clin 16:808, 1942.
46. HERMAN LM BRUS, MARTIN AFJ VAN DE LAAR, et al. Effects of patient education on compliance with basic treatment regimens and health in recent onset active rheumatoid arthritis.Ann Rheum Dis 1998; 57, 146-151.
47. HOFFMAN RW, O" SULLIVAN FX, SCAFERMEYER KR, et al: Mycoplasma infection and rheumatoid arthritis: Analysis of their relationship using immunoblotting and an ultrasensitive polymerase chain reaction detection method. Arthritis Rheum 40:1219, 1997.
48. HUKISSON EC. Measurement of pain. J Rheumatol 1982; 9:768-9.
49. IONESCU RUXANDRA, BĂLĂNESCU ANDRA. Esenţialul în reumatologie; Poliartrita reumatoidă şi boli înrudite. Editura medical Amaltea 2006. 227.
50. ISENBERG DA, MADDISON PJ, WOO PATRICIA, şi colaboratorii, Oxford Textbook of Rheumatology, Oxford University Press ed, 2004;
51. JOHANNES WJ BIJLSMA, JOSE ANTONIO P DA SILVA, ERIC HACHULLA, MICHAEL DOHERTY, ANDREW COPE, FREDERIC LIOTE: Textbook on Rheumatic Disease, BMJ Group, 2012; 206
52. JOHN H, KITAS G, TOMS T, et al. Cardiovascular co-morbidity in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2009; 23: 71-82.
53. KAARELA K, KAUTIAINEN H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. J Rheumatol. 1997, 24:1285-7.
54. KAMINA P., FRANCKE J.P. - Artrologe de membres. Description et fonction. Ed. Maloine, Paris, 1999, pag. 75-114.

55. KARLSSON EW, LEE IM, COOK NR, et al. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis Rheum 1999;42.
56. KARLUND M, OSTERGAARD M, JENSEN KE, et al. Magnetic resonance imaging, radiography, and scintigraphz of the finger joints: one year follow up of patients with early arthritis. The TIRA Group . Ann Rheum Dis 2000; 59:521.
57. KELLGREN JH LAWRENCE JS. Rheumatoid arthritis in a population sample. Ann Rheum Dis 1956; 15;1-11.
58. KELLGREN JH, BIER F. Radiological signs of rheumatoid arthritis: a study of observer differences in the reading of hand films. Ann Rheum Dis. 1956: 15:55-60.
59. KELLY C, BAIRD G, FOSTER H, et al: Prognostic significance of paraproteinaemia in rheumatoid arthritis. Ann Rheum Dis.50:290-294, 1991.
60. KIRK JA, ANSLL BM, BYWATERS EG. The hypermobilty syndrome. Musculoskeletal complaints associated with generalized joint hypermobility. Ann Rheum Dis 1967. 26:419.
61. KIRWAN JR. Natural evolution of rheumatoid arthritis. J Rheumatol 1999; 26: 720-25.
62. KIRWAN JR. The relationship between synovitis and erosions in rheumatoid arthritis. Br J Rheumatol 36: 225-228, 1997.
63. KLARESKOG L, PADYUKOV L, et al: Genes, environment and immunity in the development of rheumatoid arthritis. Curr Opin Immunol 2006; 18:650-5.
64. KLIPPEL JH, DIEPPE PA. Practical Rheumatology. 2nd ed. London: Mosby International, 1998.
65. KOH ET, SEOW A, et al. Cross cultural adaptation and validation of the Chinese Health Assessement Questionnaire for use in rheumatoid arthritis. J Rheumatol 1998; 25: 1705-8.
66. KOOP S, ALSTERGREN P. 2002. Mediators Inflamm; Blood serotonin and joint pain in seropositive versus seronegative rheumatoid arthritis; 11:211-7.
67. KU IA, IMBODEN JB, HSUE PY, et al. Rheumatoid arthritis: model of systemic Inflammation driving atherosclerosis. Circ J 2009; 73:977-85.
68. LABORATOR SYNEVO. Referinţele specifice tehnologiei de lucru utilizate. 2006. Ref Type: Catalog.