STUDY ON THE CLINICAL CHANGES IN GENERAL AND ORAL STATUS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis (RA) and periodontitis use similar destructive mechanisms; the pattern of inflammatory cells and proinflammatory cytokines that lead chronic bone erosion to RA and chronic tissue destruction in periodontitis are similar. It is argued that periodontitis could be a factor in initiating and maintaining autoimmune inflammatory responses that arise in RA. This study proposes an examination of the local inflammatory status by evaluating Quigley Hein, GI Lõe and Silness, papillary bleeding index (PBI) and CPITN, accompanied by a detailed assessment of systemic status in patients with rheumatoid arthritis. In the retrospective study, 220 patients were admitted to the Clinical Recovery Hospital in Iasi with a definite diagnosis of rheumatoid arthritis. In terms of dental-periodontal health indices, we used the following indices: Quigley Hein, GI Lõe and Silness, papillary bleeding index (PBI) and CPITN. The study was observational, retrospective, and attempted to establish the cumulative risk factors underlying the evolution of oral pathology in patients with rheumatoid arthritis. In 20.3% of patients, the higher Quigley Hein plate index significantly correlated with a higher VAS. In approximately 20% of patients, the higher Quigley Hein index significantly correlated with a higher number of painful joints, and in 27.5% of patients with swollen joint counts. Approximately 19% of patients associated higher individual values of the Quigley Hein plaque index with higher scores of DAS28. In 41% of patients, the Lõe and Silnes GI index increased significantly with a higher VAS level. In 25.8% of patients, the Lõe and Silnes GI index increased significantly with a higher number of painful joints and 30.5% of patients with swollen joint counts. A significant number of patients experienced rheumatoid factor and antiCCP antibodies, which could have significant effects on periodontal status. Also, in a significant number of patients, the individual VSH and CRP values exceeded the maximum reference limit, the mean level being significantly higher in the advanced stages of rheumatic disease, values that may exert adverse effects on periodontal health but also increase the overall inflammatory burden in the body.

Keywords: *dental-periodontal status, rheumatoid arthritis, oral health index, inflammation*

Introduction

Rheumatoid arthritis (RA) and periodontal disease are two common chronic inflammatory diseases that affect people around the world. The development of both diseases simultaneously brings considerable consequences in the public health plan and the quality of life of the affected persons [1].

There may be a non-causal association between periodontitis and RA due to common genetic and environmental risk factors [2,3]. Despite the differences in

initial etiological mechanisms, evidence from numerous clinical and epidemiological studies suggests an association between RA and periodontitis [4]. Compared to the general population, patients with periodontitis have an increased risk of developing RA and vice versa; periodontitis is at least 2 times more frequent in patients with RA [5]. In addition, the clinical course of periodontitis in patients with RA is more severe and is independent of age, gender, ethnicity or smoking history compared to non-RA individuals [6]. Furthermore, RA and periodontitis use similar destructive mechanisms, the pattern of inflammatory cells and proinflammatory cytokines leading chronic erosion to RA and chronic tissue destruction in periodontitis being similar [7-9]. New findings support the idea that periodontitis could be a factor in initiating and maintaining autoimmune inflammatory responses that occur in the RA [10].

RA is a systemic autoimmune disease characterized by chronic joint inflammation, progressive destruction of articular cartilage and bone erosion, eventually leading to loss of joint integrity [11].

There are four distinct stages of progression of rheumatoid arthritis.

Stage 1: This early stage involves initial inflammation in the joint capsule and swelling of the synovial tissue. This induces clear symptoms of joint pain, swelling and stiffness.

Stage 2: Inflammation of the synovial tissue becomes severe enough to cause cartilage lesions, the symptoms of loss of mobility and the range of movements become more common.

Stage 3: Severe rheumatoid arthritis, inflammation in the synovium destroys not only the cartilage of the joint but also the bone. Potential symptoms of this stage include increased pain and swelling and a further decrease in mobility and even in muscle strength. Physical deformities of the joint may begin to develop.

Stage 4: In the final stage of rheumatoid arthritis, the inflammatory process stops and the joints stop working altogether. Pain, swelling, stiffness and loss of mobility are still the primary symptoms at this stage.

RA behaves differently in different people and should indeed be considered a syndrome with common manifestations. The common final pathway includes persistent synovial inflammation and impaired cartilage and bone function but different subsets of diseases can be separated by clinical phenotype (for example erosion or extra-articular manifestations), particularly by the presence or absence of "specific" autoantibodies (rheumatoid factor - RF) and antibodies against citrulline peptides [ACPA]) [12].

Aim the study

This study proposes an examination of the local inflammatory status by evaluating periodontal indexes Quigley Hein, GI Lõe and Silness, papillary bleeding (PBI) and CPITN, accompanied by a detailed assessment of systemic status in patients with rheumatoid arthritis.

Materials and method

In the retrospective study, 220 patients were admitted to the Clinical Recovery Hospital in Iasi with a definite diagnosis of rheumatoid arthritis. Patients with periodontal therapy or antibiotics in the last 6 months were excluded from the study. In each case, the onset of symptoms, including some associated symptoms, general condition, clinical signs at admission, paraclinical parameters, associated conditions, and treatment were evaluated.

Patients were also clinically examined from a periodontal point of view.

The periodontal examination is performed by inspection and palpation. During the inspection we analysed the following parameters: the colour of the free gingiva and attached gingiva; surface appearance; gingival volume; periodontal biotype; evaluation of recessions with the periodontal probe between the following: enamel-cement junction and free gingival margin.

Palpation in the periodontal examination is done with the periodontal probe; we used the Williams-type I periodontal probe and the electronic probe (PaOn, orangedental, GmbH & Co. KG) to obtain the electronic periodontal chart. Through the periodontal survey we evaluated the attachment loss (probing depth); this was done for each tooth in 6 sites: disto-vestibular, centro-vestibular, mesio-vestibular, disto-orally, centro-orally, mesio-orally.

In terms of dental-periodontal health indices, we used the following indices: Quigley Hein, GI Lõe and Silness, papillary bleeding (PBI) and CPITN.

The study was observational, retrospective, and attempted to establish the cumulative risk factors underlying the evolution of oral affection in patients with rheumatoid arthritis.

The data were uploaded and processed using statistical functions in SPSS 18.0 at the significance threshold of 95%.

Primary processing, systematization of data by centralization and grouping, led to the achievement of primary indicators, which are presented as absolute measures.

On the basis of primary indicators, by means of different statistical methods of comparison, abstraction and generalization, derived indicators were obtained. The derived indicators have the role of highlighting the qualitative aspects of an assembly, addressing the relationship between different parts of a patient population or different characteristics, interdependence relationships between variables. The following derived indicators, described by the ANOVA test: average values (mean, median, module, minimum and maximum values, etc.) and dispersion indicators (standard deviation, standard error, variance coefficient) were used.

Skewness or Kurtosis tests (-2 <p <2) are tests that measure the normality of the set of values to determine whether the variables are continuous or not.

Results

Gender distribution was predominantly female (84.5%), sex ratio F / M = 5.5 / 1. Skewness / Kurtosis (-2 <p <2) suggests that the age range was homogeneous, showing variations from 18 to 85 years, with a median of about 60 years and an average of 59.40 ± 12.70 years.

In the case study, 50.9% of patients with rheumatoid arthritis were in stage III and 36.4% in stage IV.

VAS (Analog Visual Scale) is a measuring instrument, often used in epidemiological and clinical research to measure the intensity or frequency of different symptoms. For example, the amount of pain a patient feels varies along a zero continuum to an extreme amount of pain. Using a ruler, the score is determined by measuring the distance (mm) on the 10 cm line of the "no pain" point and the patient's mark, providing a score range of 0-100. The VAS pain assessment score varied between 10-90, averaging 36.55 ± 21.17, which indicated the study group as a moderate pain perception.

The number of painful joints (NPJ) varied amply (CV 96%) from 0 to 28 painful joints.

Depending on the clinical stage, the following aspects were found (p = 0.029):

- the mean mean number of painful

joints correlated with stage II polyarticular polyarthritis (7 ± 5.4);

- Stage III and IV patients had on average about 5 painful joints.

The number of swollen joints (NSJ) varied amply (CV 180%) from 0 to 21 swollen joints. The mean number of larger swollen joints correlated with Stage II rheumatoid polyarthritis (2.31 ± 2.69).

The DAS28 score (disease activity score) is a measure of disease activity in rheumatoid arthritis, and number 28 refers to the 28 examined joints. There is a wide range of disease activity measures taken into consideration in this score, including: joint examination for swelling and tenderness, global pain scores and general condition, blood markers of inflammation (eg VSH and CRP), questionnaires (eg HAQ which evaluates the function), X-ray and newer imaging techniques, such as ultrasound and MRI.

DAS28 is a composite score, the results are then entered into a complex mathematical formula to produce the overall score of disease activity. A DAS28 greater than 5.1 involves an active disease status, less than 3.2 low disease activity and less than 2.6 is an indication of remission.

86.4% of patients had positive rheumatoid factor. The correlation of rheumatoid factor positivity with staging of rheumatoid arthritis revealed that 52.6% of patients with positive rheumatoid factor were in stage III disease and 36.8% in stage IV (p = 0.014).

63.6% of patients had positive anti-CCP antibodies. Correlation of the antiCCP Ac positivity with staging of rheumatoid arthritis revealed that 51.4% of the patients with positive anti-CCPs were in the third stage of the disease and 34.3% in the fourth stage.

VSH varied in amplitude (CV 74%) from 1 to 112 mm / 1h, in 48.2% of patients the individual values exceeded the maximum reference limit (2-25 mm / 1h), the mean level being significantly higher in the more severe stages (7.0 stage I, 28.16 stage II, 35.92 stage III and 33.58 mm / 1h , p = 0.045).

CRP varied (CV 120%) in the range 0 to 8.45 mg / dl, in 46.3% of patients, the individual values being the maximum reference limit (0-1 mg / dl), the mean level exceeding the level of 1 mg / dl regardless of staging of rheumatoid arthritis (1.40, 1.98, 1.23 and 1.66 mg / dl, p = 0.162).

Total proteins varied (CV 10%) in the range of 2.10 to 8.50 g / dl, in 5% of patients, the individual values were below the baseline and 1.8% above the maximum (6.4-8, 3 g / dl), the mean level being significantly lower in the advanced stages of the disease (8.50, 7.42, 7.25 and 6.94 g / dl respectively, p = 0.045).

The Quigley Hein Plaque Index could not be determined in 12 patients (5.5%) because they were totally edented. This parameter varied (CV 29.9%) in the range of 0.80-4.50, the average level of 2.78 ± 0.83 expressing that the bacterial plaque had a width greater than 1 mm and covers up to one-third of the tooth surface irrespective of the patient's rheumatoid arthritis stage (p = 0.645) (Table 1).

Table I. Descriptive Indicators of the Quigley Hein Plaque Index Depending on Staging of Rheumatoid Arthritis

RA Stage	N	Mean	Standard Deviation	Standard Error	Confidence Interval 95%		Min	Max	F_{ANOVA} test
					-95%CI	+95%CI			
I	2	3,10	0,00	0,00	3,10	3,10	3,10	3,10	
II	24	2,81	0,98	0,20	2,40	3,22	1,30	3,90	
III	104	2,83	0,79	0,08	2,68	2,99	,80	4,10	0,654
IV	78	2,69	0,86	0,10	2,50	2,89	1,30	4,50	
Total	208	2,78	0,83	0,06	2,67	2,89	0,80	4,50	

In 20.3% of patients, the higher Quigley Hein plate index correlated significantly with a higher VAS (r = +0.203; p = 0.003).

In approximately 20% of patients, the Quigley Hein plaque index increased significantly with a higher number of painful joints (r = +0.197; p = 0.004), and in 27.5% of patients with swollen joint counts r = +0.275, p = 0.001).

Approximately 19% of patients associated higher individual values of the Quigley Hein plaque index with higher scores of DAS28 (r = +0.187; p = 0.007).

The GI index of Löe and Silnes varied (CV 30%) in the range of 0.50-3, the mean of 1.91 ± 0.57 expressing that regardless of the stage of rheumatoid arthritis in which the patient is present, the gum has an inflammation moderate, erythema, glomerular edema, bleeding at probe pressure (p = 0.645) (Table II)

Table II Descriptive Indicators of Löe and Silnes Gingival Index (GI) Depending on Staging of Rheumatoid Arthritis

RA Stage	N	Mean	Standard Deviation	Standard Error	Confidence Interval 95%		Min	Max	F_{ANOVA} test
					-95%CI	+95% CI			
I	2	2,10	0,00	0,00	2,10	2,10	2,10	2,10	
II	24	1,65	0,62	0,13	1,39	1,91	0,70	2,60	
III	104	1,97	0,57	0,06	1,86	2,08	0,50	3,00	0,654
IV	78	1,90	0,56	0,06	1,78	2,03	0,60	2,80	
Total	208	1,91	0,57	0,04	1,83	1,99	0,50	3,00	

In 41% of patients, the Loe and Silnes index significantly correlated with a higher VAS level (r = +0.410, p = 0.001) and in 25.8% of patients it correlated more significantly with a higher number of painful joints (r = +0.258; p = 0.001), and in 30.5% of patients with the number of swollen joints (r = +0.305; p = 0.001).

33.4% of patients associated higher individual GI values of Löe and Silnes with higher scores of DAS28 (r = +0.334, p = 0.001).

The PBI index varied amply (CV 35%) in the range of 0.20-3.80, the mean level of 2.22 ± 0.78 expressing that regardless of the rheumatoid arthritis stage in which the patient is situated, a fine line of bleeding or several bleeding points at the gingival margin were evident (p = 0.007) (Table III).

Table III Descriptive Indicators of the PBI Index Depending on Staging of Rheumatoid Arthritis

RA Stage	N	Mean	Standard Deviation	Standard Error	Confidence Interval 95%		Min	Max	F_{ANOVA} test
					-95%CI	+95% CI			
I	2	2,90	0,00	0,00	2,90	2,90	2,90	2,90	
II	24	1,75	0,75	0,15	1,43	2,07	0,20	2,90	
III	104	2,32	0,76	0,07	2,17	2,47	0,30	3,80	**0,007**
IV	78	2,20	0,78	0,09	2,03	2,38	0,90	3,80	
Total	208	2,22	0,78	0,05	2,11	2,32	0,20	3,80	

In 42% of patients, the higher PBI index correlated significantly with a higher VAS level (r = +0.420, p = 0.001).

In 30.8% of patients, the higher PBI index correlated significantly with a higher number of painful joints (r = +0.308; p = 0.001), and in 26.8% of patients with the number of swollen joints (r = +0.268, p = 0.001).

34.7% of patients associated higher PBI indices with higher scores of DAS28 (r = +0.347, p = 0.001).

The CPITN varied (CV 22%) in the range 1-4, the mean of 3.07 ± 0.68 suggests that regardless of the rheumatoid arthritis stage in which the patient is present, the presence of gingival bleeding, supra / subgingival calculus and increased pocket depth is noticeable (p = 0.679) (Table IV).

In approximately 25% of patients, the higher CPITN index correlated significantly with a higher VAS (r = +0.249; p = 0.001).

In 25.4% of patients the higher CPITN index correlated significantly with a higher number of painful joints (r = +0.254, p = 0.001), and in 20.3% of patients with the number of swollen joints (r = +0.203; p = 0.003).

30.3% of patients associated higher individual CPITN values with higher scores of DAS28 (r = +0.303; p = 0.001)

Table IV Descriptive Indicators of the CPITN Index Depending on Staging of Rheumatoid Arthritis

RA Stage	N	Mean	Standard Deviation	Standard Error	Confidence Interval 95%		Min	Max	F_{ANOVA} test
					-95%CI	+95%CI			
I	2	3,00	0,00	0,00	3,00	3,00	3,00	3,00	0,679
II	24	2,99	1,04	0,21	2,55	3,43	1,00	4,00	

III	104	3,13	0,60	0,06	3,01	3,24	1,60	4,00	
IV	78	3,02	0,66	0,07	2,87	3,17	1,30	4,00	
Total	208	3,07	0,68	0,05	2,98	3,16	1,00	4,00	

Discussion

Rheumatoid arthritis is a chronic inflammatory disease of the joints characterized by loss of connective tissue and mineralized structures, the so-called "synovial membrane". It affects about 1% of the world's population. It affects women about three times more often than men. Prevalence varies from 0.2% to 1.0% in different European, North American, Asian and Australian populations. The prevalence of periodontal disease increased twice in patients with rheumatoid arthritis versus the general population [11,13].

Synovial inflammation and of the adjacent soft tissues may be initiated by a number of microbial factors, including bacterial DNA, heat shock proteins and lipopolysaccharides. MMP, cathepsins and osteoclast activation also contribute to bone resorption, moreover, a number of cytokines, such as TNF-α, IL-1 and macrophage colony stimulating factor (MCSF), are also involved. Epigenetic changes by regulating the proinflammatory response by modulating NF k B that affect TNF-α can be crucially involved in the pathology of RA and other chronic inflammatory diseases [4, 14, 15].

Chronic periodontitis and RA seem to share many common pathological features [3,16]. Oxygen metabolism plays an important role in the pathogenesis of both diseases. There are many studies stating that oxidative stress plays a major role in the pathogenesis of autoimune diseases, including RA [17,18], however, some studies state that the presence of RA seems to not affect the values of the local and systemic oxidative stress index in patients with chronic periodontitis [19-22]. RA may affect any joint, but is usually found in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as in the knee. Clinical presentation of RA varies, but the insidious discovery of pain with symmetrical swelling of small joints is the most common discovery. RA is acute or subacute in about 25% of patients, but its presentation patterns also includes palindromic onset, mono-articular presentation, extraarticular synovitis, polyalgic onset and general symptoms. Duration of morning stiffness is related to disease activity [11,23].

It is now clear that most cases of RA are triggered by an autoimmune response to citrullinated proteins [24]. Such proteins are generated under physiological conditions, but the loss of tolerance in genetically sensitive individuals initiates the generation of autoantibodies to citrullinated proteins (ACPA) in the synovium and the subsequent development of rheumatoid arthritis [25].

In this study, we noticed a prevalence of female gender involvement, which had a significant severity of rheumatoid arthritis (Stages III - 53.8% and IV - 36.6%), while a relevant frequency of more mild cases was observed in the male sex - stage I patients 5.9% male vs 0% female and stage II 23.5% male vs 9.7% female.

Serum levels of VSH and C-reactive protein (CRP) recorded 48.2% of patients individual values of these two parameters above the maximum baseline, the mean being significantly higher in the advanced stages of the disease [26].

This quantification of inflammatory markers, which are witnesses of an

exacerbated inflammatory status, with negative effects on periodontal homeostasis, should not be neglected [3,8,27].

Regarding periodontopathogenic bacteria, *P. gingivalis* has been linked to RA through its specific enzimatic properties which contribute to the production of citrullinated peptides that determines an immune response which could be responsible for the severe course, or even as a cause for the developement of RA [28-30].

An extremely high percentage of patients (86.4%) had positive rheumatoid factor (RF), this marker has been found in rheumatoid arthritis and other chronic inflammatory diseases, including periodontal disease. Rheumatoid factor may be present in the gingival tissues, in subgingival plaque, and in the periodontal serum of patients [31]. Patients with seropositive RF periodontal disease had a high concentration of IgG and IgM antibodies against oral microorganisms compared to seronegative patients thus contributing to the overall exacerbates inflammatory burden of these patients [32].

A significant number of patients (63.6%) presented anticyclic citrullinated peptide antibodies (antiCCP), moreover, the correlation of the antiCCP positivity with the staging of rheumatoid arthritis revealed that 51.4% of patients with positive anti-CCPs were in stage III disease and 34.3% in stage IV ($p = 0.451$).

In a meta-analysis, Fuggle et al. [33] found that oral hygiene parameters, the gingival index, were significantly higher in RA patients than in healthy subjects in the control groups; however, this finding is not repeated in regard to the plaque index, another parameter of oral hygiene. There was a significant mean loss of teeth in RA cases compared to controls (MD: 2.46, CI 95: 0.30, 4.63). The main finding that there is an increased risk of periodontitis in RA patients compared to healthy controls is consistent with the findings of systematic reviews. In 2015, Araújo et al. have published a critical assessment of studies investigating the relationship between RA and periodontitis [9]. There have been selected articles published since 2012, including eight epidemiological studies, four periodontal intervention studies, and five investigating the role of inflammatory mediators in both diseases. They found that 21 studies demonstrated an association by statistical analysis and 3 studies demonstrated an association through descriptive analysis between RA and periodontitis.

Taking into account the oral hygiene status, in approximately 20% of patients the Quigley Hein plaque index increased significantly with a higher number of painful joints ($p = 0.004$) and in 27.5% of the patients with the number of joints swelling ($p = 0.001$). Also, in 25.8% of patients, the Löe and Silnes GI index increased more significantly with a higher number of painful joints ($p = 0.001$), and in 30.5% of the patients with the number of swollen joints ($p = 0.001$). We also noticed the same for the papillary bleeding index (PBI) and CPITN. Thus, we can clinically correlate the periodontal inflammatory status with exacerbated joint damage which is an indicator of the active status of RA.

To maintain oral health, patients with RA are encouraged to achieve proper oral hygiene under close monitoring of a specialist and consultation of the periodontist is necessary to determine the correct course of treatment. Reducing oral contribution to the overall inflammatory burden to achieve a favourable outcome of periodontal treatment is an important desideratum. Maintaining the full health of RA patients should be a collaborative effort so it is important for dentists and rheumatologists to work together when

treating a patient with RA. This partnership will certainly influence the oral and global health of these patients for the better [1].

In the present study, the most frequent and the most severe rheumatoid injury was found in female subjects. Also, a significant degree of RA was encountered at ages over 60 years.

The pain perception recorded by the VAS score showed moderate intensity without significant differences between sexes or age groups. The mean high value of painful and swollen joints correlated with Stage II rheumatoid polyarthritis.

A significant number of patients experienced rheumatoid factor and anti CCP antibodies, which could have significant effects on periodontal status [34,35].

Also, in a significant number of patients, the individual VSH and CRP values exceeded the maximum reference limit, the mean level being significantly higher in the advanced stages of rheumatic disease, values that may exert adverse effects on periodontal health.

Conclusions

Periodontal parameters (hygienic index, index of gingival inflammation, papillary bleeding index and CPITN) correlated significantly with an increased number of painful and swollen joints; this provides indications of clinical correlation of periodontal inflammatory status with exacerbated joint impairmen.

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