THE ASSOCIATION BETWEEN RHEUMATOID ARTHRITIS, PERIODONTITIS AND ISCHEMIC HEART DISEASE

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Abstract: *Patients with active rheumatoid arthritis (RA) have a significantly higher incidence of gum disease compared with healthy subjects, in RA patients the correlation with tooth and alveolar bone loss being demonstrated. It is interesting to study the relationship between the rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti CCP), and Porphinomonas gingivalis (Pg), RF and anti CCP, present in RA, these being identified in the gum and in the subgingival plaque as well. The presence of gum disease increases the chance of developing heart disease, and mortality from cardiovascular damage in patients with RA, is 2 times higher compared to the general population. Based on these observations the question, whether oral infections play an important role in the pathogenesis of rheumatoid arthritis, and whether cardiovascular disease increases the risk in these patients, arises.*

Cuvinte cheie: *poliartrită reumatoidă, parodontoză, boală cardiacă ischemică*

Rezumat: *Pacienții cu poliartrită reumatoidă (PR) activă au o incidență semnificativ crescută a afectării gingivale în comparație cu subiecții sănătoși, la pacienții cu PR fiind demonstrată corelația cu pierderea dinților și a osului alveolar. Este interesantă studierea relației între factorul reumatoid (FR), anticorpii antipeptidă ciclică citrulinată (atc anti CCP) și Porphinomonas gingivalis (Pg), FR și atc anti CCP, prezenți în PR, fiind identificați și în gingie și placa subgingivală. Prezența afecțiunilor gingivale crește șansa de apariție a bolilor cardiace, iar mortalitatea prin afectare cardiovasculară la pacienții cu PR este de 2 ori mai mare față de populația generală. Pornind de la aceste observații se ridică întrebarea dacă infecțiile orale joacă un rol important în patogenia poliartritei reumatoide și dacă acestea augmentează riscul de boală cardiovasculară la acești pacienți.*

INTRODUCTION

Clinical research studies have shown that certain environmental factors induce specific effects related to the pathogenesis of rheumatoid arthritis (RA) and periodontal disease (PD) while others develop nonspecific effects, triggering and perpetuating the inflammatory process.(1,2) Although RA is a disease predominantly affecting joints, and PD a gingival tissue disease, it is shown that the presence of gum disease increases the chance of developing heart disease, and impaired cardiovascular mortality at patients with RA is 2 times higher compared to the general population.(3-8) RA, an immune inflammatory disease and PD, a gingival tissue disease, are characterized by an immune response and similar tissue degradation.(3,4) The association between RA and PD has been demonstrated by studies conducted in the last decade, which showed that patients with active RA have a significantly higher incidence of gum damage compared with the healthy subjects, at patients with RA the correlation of the teeth and the alveolar bone loss is shown.(8-10) It is interesting to study the relationship between the rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti CCP), and Porphinomonas gingivalis (Pg), RF and anti CCP, present in RA, these being identified in the gum and in the subgingival plaque as well.(9-11)

PURPOSE

Our study objective was to assess whether patients with RA and periodontal disease (RA+PD) have a risk to develop a higher ischemic heart disease (IHD) compared with RA patients without periodontal disease (RA-PD).

METHODS

The study included 106 patients diagnosed with RA according to ACR / EULAR 2010 criteria, in which ischemic heart disease was diagnosed after or at the moment of diagnosis of RA. 6 patients diagnosed with RA present PD (RA + PD), and 50 patients with RA, does not present PD (RA -PD).(12) Patients who presented other immune inflammatory diseases, hematologic, renal, or history of cancer, those with BMI over 30, patients with acute dysmetabolic syndromes, history of cardiovascular disease or family history of cardiovascular disease in first degree relatives were excluded. The duration of the disease was defined as the time from the first diagnosis (medically documented) until the evaluation visit. ECG was performed at rest (ECG in 12 deviations), with a MAC 1200 device, for diagnosis of arrhythmias, left ventricular hypertrophy, myocardial ischemia. The Sokolov-Lyon criteria for left ventricular hypertrophy, ECG diagnosis were used. We conducted a physical examination of patients, recorded medical history, a positive family history, the living and working conditions. Weight was measured, laboratory investigations were determined "a jeune", BP was determined after a 5 minutes seated rest. Erythrocyte sedimentation rate (ESR) was measured with an Automated Sedisystem, ESR≥28mm/h being considered to have a positive value. For antibodies we used Elisa method,

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different kits: QuantaLite™CCP3 IgG Elisa, for anti CCP; and for RF the latex method. Normal value was considered under 23UI/ml for anti CCP, and under 14UI/ml for RF. C-reactive protein (CRP) was determined by nephelometry, considered to be positive, having a value of over 6mg/dl.

The Framingham score was calculated (FS) using the model proposed by the Joint National Committee on Blood Pressure and the National Cholesterol Education Program in order to assess the risk of coronary disease. Age, total cholesterol, HDL cholesterol, blood pressure, the presence or absence of smoking were taken into consideration when calculating FS.(13,14)

Ischemic heart disease – was stratified into groups (0-3) using family history, medical history of the patient and ischemic pathognomonic ECG changes as follows:0- No ischemic pathognomonic ECG changes, without typical history of angina, without a history of MI; 1- Pathognomonic ECG changes of myocardial ischemia, with no description of angina, without a history of MI; 2-Typical angina description, with or without ECG changes, but without ECG signs or history of MI; 3- IM history, ECG documented, anamnestic or through medical documents – discharge summary. The presence of PD (periodontal disease and / or dental infections) was assessed by the dental specialist, appreciating the gingival level, scaling and the presence of cavities.

Statistical analysis

Statistical analysis was performed using SPSS, version 17 and GRAPH Pad Prisma. For univariate analysis of data the T test was used for independent variables, the Z test for comparison of two proportions and correlation based on the Pearson correlation coefficient. Multivariate analysis was performed by calculating the multivariate regressions. We used frequency grids to obtain numerical data and percentages. Mean and standard deviation (SD) were calculated. Statistical significance was considered at a value of $p < 0.05$.

RESULTS

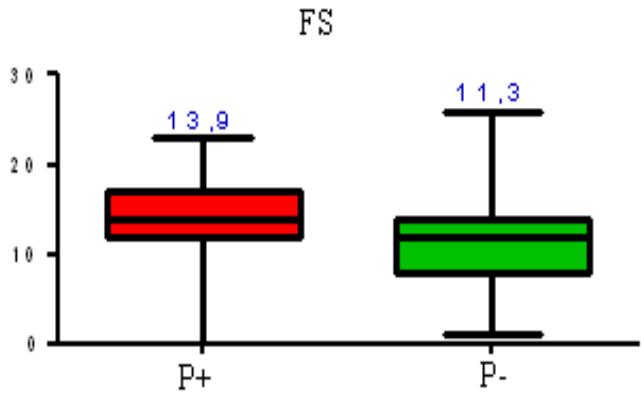
The study group included 106 patients, out of which 17% men and 83% women, with a mean age of 57.3 years at patients diagnosed with RA who associated PD (RA+PD), 50.5 years in patients with RA but without signs of PD (RA - PD). The mean duration of the arthritis disease was 7,14±5,23 years at those with RA+PD, in comparison with 5,24±4,85 years at pacients with RA - PD. The proportion between patients from urban/rural areas was approximately equal, and the level of schooling compared to the average tuition (middle school/high school/higher education) was similar in the two groups of patients. The characteristics of the study group are presented in Table no. 1.

Table no. 1. Characteristics of the study group

Number of patients	PR+BP 56	PR-BP 50	Statistical significance
Age (mean, years)	5 7,3	50,5	p=0,016
Men **Women**	12 44	6 44	p=0,19
Urban **Rural**	32 24	31 19	p=0,61
Schooling	36/20	32/18	p=0,98
Smoking **Current smokers/** **Former smokers/** **Non-smoking**	5/9/42	10/11/29	p=0,14
ESR <28mm/h **≥28mm/h**	36 20	33 17	p=0,28
CR ≤6mg/dl/ **>6mg/dl**	6/47	17/33	p=0,032
RF **positive/negative**	10/46	10/40	p=0,80
Atc.CCP **positive/negative**	22/34	22/28	p=0,08
Framingham Score **(mean+SD)**	13,9	11,3	p=0,001
Cardiac affection **0** **1** **2** **3**	 10 25 16 3	 24 16 10 0	p=0,003
Duration of illness **(years±SD)**	7,14±5,23	5,24±4,85	p=0,05

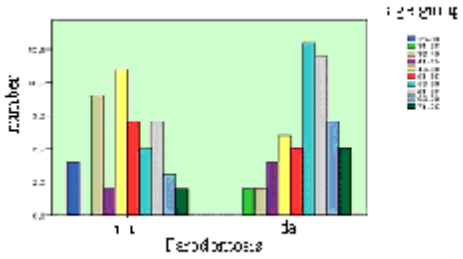
The presence of ischemic heart damage significantly correlated with the presence of PD in patients with RA, and FS had a higher average in these patients, as shown in Figure no. 1.

Figure no. 1. The value of Framingham score in patients diagnosed with rheumatoid arthritis in relation to the presence or absence of periodontal disease



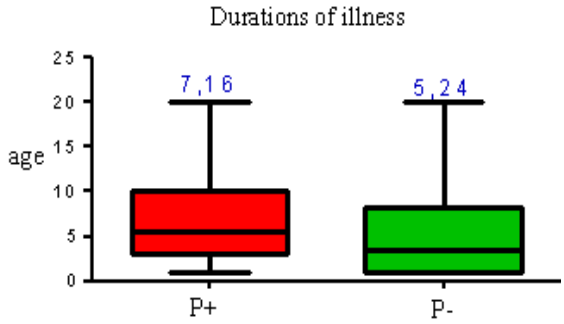
The distribution of periodontal disease by age is presented in figure no. 2, mentioning the fact that the mean age of patients RA+PD is significantly higher than in patients with RA- PD.

Figure no. 2. The distribution of periodontal disease by age



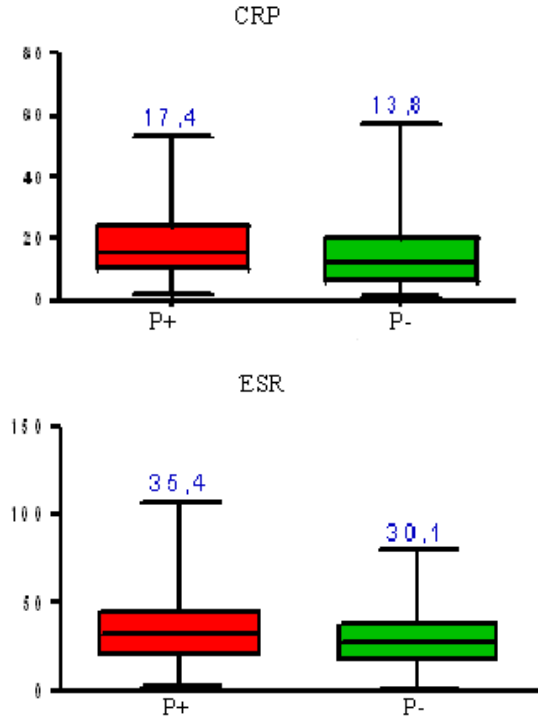
The average evolution of RA was statistically significantly higher in the RA+PD group than in the RA-PD group as shown in figure no. 3.

Figure no. 3. The average duration of rheumatic disease in patients with / without periodontal disease



Systemic inflammation assessed by CRP and ESR was more highly expressed in the RA+PD group than in the RA-PD group, although the statistical significance was small and only present for CRP as shown in figure no. 4.

Figure no. 4. Markers of inflammation in patients with rheumatoid arthritis in relation to the absence/presence of periodontal disease: C- Reactive Protein CRP, ESR, Erythrocyte Sedimentation Rate



DISCUSSIONS

Assuming that cardiovascular disease is the leading cause of morbidity and mortality in RA patients and PD is an associated risk factor in determining coronary artery disease, we conducted this study in order to clarify the implications of PD in patients with RA, trying to determine the risk factors that predispose patients with RA in developing PD. Recently WHO has stressed the importance of oral health in terms of impact on the health of the body, the PAVE-Periodontitis and Vascular Eventsstudies demonstrating the usefulness of oral hygiene assessment in terms of reducing cardiovascular disease risk.(7)

Systemic inflammation present in active forms of RA is found in the periodontal impairment as well being responsible for the destruction of the periodontal tissue and the alveolar bone, with direct implications on coronary arteries. Quantifiable markers of the CRP and ESR inflammations were found in a proportion of 83,9% and 64,2% in RA+ PD patients the presence of PCR being a predictive factor for CVD in patients with RA who associate PD with p = 0.032.(4,15)

Although there are studies showing that habits such as smoking have a predictive role in developing cardiovascular disease and in patients with RA a high prevalence of smoking and poor oral hygiene was found, it is insufficiently evaluated in practice by rheumatologists.(16-18) In our study we did not find a combination in RA+PD patients, possibly due to the relatively small number of patients and/or provided that under the influence of educational measures, the number of smokers appears to decrease, the number of the female smokers tend to increase, and few women stop smoking.

Some clinical trials have tried to explain whether there is an association beween RA and PD, ischemic heart disease (19), assuming that both RA and PD are characterized by chronic systemic inflammation and therefore increase the risk of cardiovascular disease. In this study BCI is significantly associated with the duration of the disease, FS, and the presence of CRP.

In patients with immune inflammatory disease coronary risk assessment scores are underestimated, thus EULAR Standing Committee for Clinical Affairs (ESCCA), proposed to adjust these scores depending on the clinical biological particularities.(20-22) Thus recommendation No. 4 states: calculation of cardiovascular risk scores must be multiplied by 1.5 in patients with RA where the duration of the disease lasts more than 10 years, RF and/or anti CCP positive and show extraarticular manifestations.(22)

Even though we did not find statistically significant association, possibly due to the relatively small number of patients studied, it is proved that the rheumatoid factor present in the serum of RA pacients, has been identified at the level of the gum and subgingival plaque.(2-4) Oral pathogen agents are responsible for producing anti P.gingivalis antibodies closely correlated with protein citrullination in RA+PD patients.(23,24)

CONCLUSIONS

RA+PD patients are more exposed to ischemic heart disease, the duration of the rheumatoid disease and the age of patients with RA demonstrating this fact. Cardiovascular risk assessment scores in patients with immune inflammatory diseases are becoming useful, in the prediction of a possible cardiovascular disease in these patients. To accurately determine the magnitude of cardiovascular risk factors associated with rheumatoid arthritis and gum damage, and to establish strategies for prevention extensive research studies are still required.

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