Porphyromonas Gingivalis - A Periodontal Pathogen with Potential Role in Rheumatoid Arthritis and its Association with Anti-CCP and Anti-MCV Antibodies Positivity

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Abstract: *Background*: In recent studies, a strong association between rheumatoid arthritis (RA) and chronic periodontal disease (CPD) has been identified, indicating common disease pathogenesis and risk factors. One of them is the presence of the pathogen Porphyromonas gingivalis (PG), which can initiate the process of citrullination, by secreting the enzyme Porphyromonas Peptydil Arginine Deminase (PPAD).

The aim of the study is to show the presence of PG in RA patients, and to evaluate the association of the PG presence with anti-citrullinated proteins/peptides (ACPA) positivity i.e. anti CCP and anti MCV positivity.

Methods: The study included 80 participants - 30 patients which fulfilled 2010 ACR/EULAR RA classification criteria and 50 controls, which were genetically analyzed for the presence of PG by Chelex®100 method and polymerase chain reaction (PCR) and for the presence of anti CCP and anti MCV autoantibodies with the ELISA method.

Results: Twenty out of thirty RA patients (80 %) and 16 out of 50 controls (32%) were positive for PG. (χ 2 = 11.461, p <0.001 for OA and χ2 = 13.91, p <0.001 for HC). Of the PG-positive RA patients, 83% had positive anti-CCP and 79% had positive anti-MCV test. The odds ratios OR of 25 and 19 were statistically significant (p = 0.008 and p =0,014 respectfully).

Conclusions: PG was present more frequently in RA patients and there was a statistically significant association with anti CCP and anti MCV antibodies.

Keywords: Rheumatoid arthritis, Chronic periodontal disease, Porphyromonas gingivalis, ACPA, anti-CCP antibodies, anti-MCV antibodies.

INTRODUCTION

Bacterial cell was observed for the first time in the distant year of 1663, when Antonie van Leeuwenhoek observed bacteria he isolated from his own teeth [1]. Today, it is well known that the number of microorganisms that inhabit the human body exceeds by many times the number of its own cells [2-4]. Nowadays, there are two very important terms, microbiota and microbiome. The term microbiota defines the microbial communities in the microhabitat. It was used for the first time by Joshua Lederberg and his colleague Mc Cray in 2001, as a set of microorganisms that inhabits particular environment [5]. The human microbiota includes between 10 and 100 trillions of symbiotic bacterial cells [3]. The term microbiome was introduced and is defined as the aggregate of all microbiota and biofluids, along with the corresponding anatomical sites in which they reside [5,6]. The two terms - human microbiota and human microbiome – are used interchangeably [3]. There is a dynamic interaction between the human microbiota and human microbiome in health and disease, because of which they are considered to be an additional organ in human body [3-5,7]. However, changes in the composition of human microbial communities are associated with various chronic diseases [8,9].

The involvement of microbial communities is also suggested in the genesis of rheumatoid arthritis (RA) [2,4]. Consideration of RA as an autoimmune polygenic disease is not new, and despite its unknown etiology, it is suggested that both genetic and environmental factors including infectious agents are involved in its pathogenesis [10,11]. In this regard, the presence of microorganism in RA is detected in the oral cavity, lungs and gastrointestinal tract [12].

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E-ISSN: 2310-9874/21 **© https://doi.org/10.12970/2310-9874.2021.09.01**

One of the main pathogen microorganisms detected in the oral cavity of RA patients, who suffer from chronic periodontal disease (CPD) and tooth loss is bacteria Porphyromonas gingivalis (PG) which is a part of so called “red complex” together with Treponema denticola and Tannerella Forsythia, which is associated with advanced periodontal disease [13-18].

PG is a Gram negative, black pigmented, rod shaped oral anaerobic bacteria which secondarily colonizes dental biofilms in the human oral cavity [8,15-17]. As an obligate anaerobe, its normal habitat are the anaerobic spaces in the deep crypts of the tongue, but mainly in the sub-gingival plague in the deep periodontal pockets, invading the connective tissue of the gingiva [8,13]. Described as a key pathogen of CPD, PG possesses number of different virulent factors, which contribute to the initiation and progression of CPD and can function under conditions of both symbiotic and parasitic linkages with the host [17].

PG is the only known prokaryote which expresses the functional form of peptydil arginin deiminase (PAD) [24,26], an enzyme involved in the conversion of the arginine residues to citrulline, the process called citrullination which is very crucial for the RA pathogenesis [20,28]. PG is also associated with the production of the anti-citrullinated protein antibodies (ACPA) which are highly specific for RA and also with inflammation which is present in both diseases, CPD and RA, respectively.

This fact has prompted some of the authors to suggest the potential etiological role of PG in the development of RA through the generation of citrullinated antigens [20, 26] Studies have confirmed that the PAD of the PG, so called PPAD may induce citrullination of human peptides which happens outside of the joints [19]. Molecular mimicry between bacterial and human protein epitopes is also assumed [26].

Association showing epidemiological links between CPD and RA are shown in the results from different studies and was first time discussed on the joint seminar between European Federation of Periodontology and American Academy of Periodontology suggesting the role for PG and CPD in the development of RA [21-27]. There are many similarities between CPD and RA in the cellular, enzymatic and cytokine profiles as well as in the overexpression of matrix metalloproteinases and TNF - alpha, which indicates common internal and external risk factors such as HLA-DRB1 alleles and smoking in the pathogenesis of both diseases [23,24].

The aim of this study was to evaluate the presence of PG in gingival pockets of RA patients, to compare it with the presence of PG in controls and also to evaluate if there is any association between the presence of PG and ACPA antibody positivity in RA patients.

MATERIALS AND METHODS

RA patients were selected at the Rheumatology Department of the University of Plovdiv and Caspela Hospital, where they were examined as an outpatients. They have full filled the 2010 ACR/EULAR classification criteria for RA, defined by Aletaha and coworkers [25].

Healthy controls and OA patients were used as control groups. Healthy controls were members of the stuff without known inflammatory joint diseases. We have used patients with OA as a second control groups in order to see whether there would be an association between inflammation in OA and presence of PG, regardless of the presence of ACPA.

All participants underwent regular rheumatology examination and were referred for dental examination and evaluation of periodontal status by a specialist for CPD.

The sample for the presence of PG was taken after cleaning the supra gingival plaque, isolating and drying the corresponding tooth and carefully inserting a sterile pin (ISO40), without causing bleeding, to the bottom of the periodontal pocket medially and distally. The pins are removed after 1 minute and transported in sterile 1.5 ml Eppendorf plastic containers for analysis of periodontal pathogens from the sub gingival plaque.

Genetic analysis for the presence of PG was performed by PCR method, i.e. by isolating DNA from sub-gingival biofilm in the deep periodontal pockets of the patients and controls, because up to 80% of the bacteria inhabiting human cavities cannot be culturally identified and can only be accurately identified by methods that determine their gene sequences [2-4]. Isolation of the high molecular weight bacterial DNA from the sub-gingival plaque is performed using Chelex®100 and using polymerase chain reaction (PCR), by enzymatic amplification of selected nucleotide sequences. PCR test was originally developed in 1983 by American biochemist Kary Mullis,

who was awarded Nobel Prize in Chemistry in 1993. It is common tool used in medical and biological research as it is used in the early stages of processing DNA for sequencing, for the detecting the presence or the absence of a gene to help identify pathogens during infections (like PG) and for generating forensic DNA profiles from tiny samples of DNA. We have used it for the detection of PG in patients with RA and in controls.

Because in RA citrullination occurs in the periodontal tissue, lungs and synovium, and ACPA can target wide range of citrullinated antigens such as cyclic citrullinated peptides, vimentin, enolase, fibrinogen collagen type II, biglycan, keratin and histones, we have chosen to test antibodies for 2 cittrulinated antigens anti-cyclic citrullinated protein antibodies (Anti-CCP) and anti mutated citrullinated vimentine antibodies (anti-MCV) [29-33].

For the immunological studies for anti-CCP and Anti-MCV antibodies, venous blood (up to 5 ml) was taken from the study participants. Blood was collected in monovets without anticoagulant. Thirty minutes after blood collection, the tubes were centrifugated at 3000 rpm. Samples were stored at -20 °C before analysis for 10 min. Measurements were taken on an ELISA-Huma Reader HS, HUMAN (Wiesbaden, Germany). Immunological tests were performed according to the instructions of the manufacturers. For testing the IgG class autoantibodies against mutated citrullinated vimentin (MCV), the ELISA Kit from ORGENTEC Diagnostika, Mainz - Germany was used. The titers ≥ 20 U/ml- were considered as positive and the titers below 20 U/ml. negative. Also, for testing of anti-cyclic citrullinated peptides (CCP) IgG class autoantibodies, anti-CCP hs (high sensitivity) kits from ORGENTEC Diagnostika, Mainz - Germany were used, according to the manufacturer's instructions. The interpretation of the results obtained, were negative <20 U / ml and positive ≥ 20 U / ml, respectively.

The study was approved by the Ethics Committee of Medical University of Plovdiv № P-961/ of 15-04-2015/. Each participant has signed an informed consent to participate in the study and it was lead according to the principals of the Declaration of Helsinki.

The data obtained were analyzed with the statistical program SPSS, version 22 and $p \leq 0,05$ was considered statistically significant.

RESULTS

We have evaluated 80 participants over 18 years of age, 30 of whom were RA patients and 50 controls; 26 patients with OA and 24 HC. The demographic data of the study participants are shown in Table **1**.

The rate of positive PG test was highest in RA patients (80%), followed by OA patients (35%) and healthy controls (29%) or in total in 16 out of 50 controls (32%). Chi-square test showed that the distribution of positive findings differs significantly ($p = 0.001$), but does not determine exactly which group comparisons are statistically significant. This information was supplemented by proportionate pairwise comparisons, which found that the percentage of PG positive findings in patients with RA was significantly higher than in patients with OA ($\chi 2 = 11.461$, $p <0.001$) and by healthy controls ($\chi 2 = 13.91$, $p <0.001$). This results are shown in Table **2**.

In RA patients, the relationship between PG positivity and anti-CCP and anti-MCV positivity, was evaluated. For this purpose, a cross table was used and the odds ratio (OR) was calculated. In the context of the present study, the OR shows the association between the presence of PG and seropositivity for anti-

Table 1: The Demographic Data of the Study Participants

	Total	RA	OA	HC	Statistical significance
Age	51.+/-12.6	52.07(±12.26)	58.92(±12.25)	43.72(±2.26)	RA→OA (0.255) RA→HC (0.064) OA→HC (0.002**)
Gender					
Females	22 (28%)	10 (33%)	7 (27%)	5 (21%)	0.550
Males	58 (72%)	20 (67%)	19 (73%)	19 (79%)	
Total No	80	30	26	24	

*Statistical significance, $p \leq 0.05$; **Statistical significance, $p \leq 0.01$.
Legend RA-Rheumatoid arthritis, OA osteoarthritis, HC-Healthy controls.

Table 2: Distribution of PG Positive and Negative Findings between the Groups

	Groups			Statistical significance	Couples comparison
	RA	OA	HC	P values	P values
PG + (1)	24 (80%)	9 (35%)	7 (29%)	0.001**	RA→OA (0.000**) RA→HC (0.000**) OA→HC (0.65)
PG – (0)	6 (20%)	17 (65%)	17 (71%)		
Total No	30	26	24		

*Statistical significance, p ≤ 0.05; **Statistical significance, p ≤ 0.01.
Legend RA-Rheumatoid arthritis, OA osteoarthritis, HC-Healthy controls.
PG positive (= 1) and negative (= 0).

CCP and anti-MCV antibodies. Values equal to 0 indicate no dependency; values greater than 1 (> 1) are associated with higher likelihood of anti-CCP and anti-MCV seropositivity in patients with positive PG and values lower than 1 (<1) indicate a higher likelihood of seropositivity in patients with negative PG. The analysis was performed with the Medcalc 18.5 program. For the relationship to be statistically significant, the error value must be equal to or less than 0.05 (p ≤ 0.05).

To determine the relationship between the presence of PG and anti-CCP seropositivity, RA were divided into two groups comprising 24 patients with positive PG indicators and 6 patients with negative PG indicators. The majority, 20 out of the total 24 PG positive patients (83%) were also anti-CCP positive. The remaining 4 PG positive patients (17%) were anti-CCP negative. Only 2 out of the total 6 PG negative patients (33%) were anti-CCP positive and the remaining four (67%) patients were negative for both indicators – PG and anti-CCP. The odds ratio OR of 25 is statistically significant (p = 0.008). Based on these results, it can be concluded that in PG positive RA patients, the likelihood of anti-CCP seropositivity is significantly higher than PG negative RA patients (Table **3**).

The relationship between PG and anti-MCV seropositivity was similar to the previous analysis, again including the 30 patients with RA divided into 24 patients with positive and 6 patients with negative PG indicators.

Nineteen out of twenty four of the PG positive patients (79%) were anti-MCV positive. The remaining 5 PG positive patients (21%) were anti-MCV negative. One patient of a total of 6 PG negative patients (17%) was anti-MCV positive and the remaining 5 (83%) were negative for both indicators, PG and anti-MCV antibodies. The odds ratio OR = 19 was statistically significant (p = 0.014), meaning that in PG positive RA patients the likelihood of anti-MCV seropositivity was

Table 3: The Association between PG Presence and Anti-CCP Antibody Positivity

	Anti-CCP		Odds ratio 95% CI	P value
	Positive	Negative		
PG				
Positive	20 (83%)	4 (17%)	25 (2,25-205)	0.008**
Negative	2 (33%)	4 (67%)		

*Statistical significance, p ≤ 0.05; **Statistical significance, p ≤ 0.01.
Legend: PG –Porphyromonas Gingivalis, Anti-CCP Anti citrullinated protein antibodies CI Confidence Interval.

Table 4: The Association between PG Presence and Anti-MCV Antibody Positivity

	Anti-MCV		Odds ratio 95% CI	P value
	Positive	Negative		
PG				
Positive	19 (79%)	5 (21%)	19 (1,78-201)	0.014**
Negative	1 (17%)	5 (83%)		

*Statistical significance, p ≤ 0.05; **Statistical significance, p ≤ 0.01.
Legend: PG –Porphyromonas Gingivalis, Anti-CCP Anti citrullinated protein antibodies CI Confidence Interval.

significantly higher than PG negative RA patients. Please see Table **4**.

DISCUSSION

The present study compared the presence of PG in patients with RA and control groups, patients with OA and healthy controls. The association between PG with two serological markers from the ACPA group - anti CCP and anti MCV, was also evaluated . The highest rate of PG positivity was found in the RA patients (80%), followed by OA patients (35%) and healthy controls (29%).

The presence of severe generalized CPD, have been found in RA patients in this study, and those patients were positive for PG. They had major loss of alveolar bone, deep periodontal pockets above 6 mm, and advanced loss of teeth attachment, along with poor oral hygiene and generalized gingival bleeding. Some limitations fort this study was that pre-enrolled RA patients had a high rate of completely jagged jaws, which excluded them from the study. This was a limiting factor for the initial involvement of patients. A high rate of partial analgesia was also found in patients with RA - the present study did not present the severity of it. Also, the identification of PG was based on genetic analysis, although in studies of others serological testing, using detection of antibodies against PG, was used.

In regards with the association of the PG positivity and ACPA positivity in RA patients, this study confirmed that anti-CCP and anti-MCV positivity is significantly more common in PG positive than in PG negative RA patients.

A number of studies have focused on the relationship between PG and anti-CCP and other antibodies against citrullinated proteins/peptides. In our study, in addition to association with anti-CCP, we sought association with PG and anti-MCV antibodies, in RA patients.

Mikuls *et al*. have found significant positive correlation between PG antibody titer with anti-CCP-IgM and -IgG-in patients with RA. They concluded that the high titers of the antibodies to PG were more common in patients with RA than in healthy controls. They have found that PG antibody titers were highest in CPD, lowest in HC and intermediate in RA, with the high titers found more frequently in RA and CPD - 67% and 77%, respectively. Only 40% controls had high titers. They have proposed that infection with this organism plays a role in the risk and progression of RA, due to the open association between PG titers and related RA autoantibodies and CRP [34]. The only difference from our study was the method of detection of PG.

Our study was very similar with the study of Oluwagbemigum *et al*., who suggested that in specific subgroups of individuals with systemic inflammation, higher salivary PG DNA is associated with elevated serum ACPA, sharing the thesis about the role of PG in the development of an immune response to citrullinated proteins. They have evaluated the relationship between PG and ACPA in the German population where salivary PG DNA and serum anti-CCP2 were investigated. Participants with high PG DNA had approximately 2.8-fold higher levels of anti-CCP2 than participants with low PG DNA. Citrullinated epitopes of α-enolase and vimentin were also commonly reported as ACPA in participants with high PG DNA and increased CPP [36].

Hitchon *et al*. found that IgG class antibodies against PG were higher in patients with RA compared to their relatives and healthy controls, and also higher in ACPA-positive patients with RA than ACPA-negative patients with RA and their relatives, but comparable in RF-positive and RF-negative patients and relatives. Hitchon *et al*. concluded that in a genetically predisposed population of patients with RA and their relatives, antibodies to PG are associated with ACPA and suggest that immune responses to PG may play a role in impaired immune tolerance to citrullinated antigens [37]. The results from our study are also in accordance with this study.

Arvikar *et al*. also found a significantly higher average antibody titer level for PG in patients with RA, comparing their levels with both healthy controls and patients with lupus and other connective tissue diseases (CTD). It has also been found that in early RA, anti-CCP antibody levels are significantly higher in patients with positive antibodies to PG than in those who are negative, and the levels of PG antibodies correlate very well with the anti-CCP antibody titers [11]. Significantly higher levels of anti-PG antibodies and anti-CCP antibodies in RA patients were also found by Okada *et al*. [38].

Similar with our study, a number of studies have indicated an increased incidence of PG antibody positivity in RA patients when compared to healthy controls. However, the possible influence of the

DMARD treatment on the presence of PG and, respectively, the antibody response to them in long-running RA, is also indicated [11]. Ogrendik *et al*. found significantly higher levels of IgG to PG in patients with RA compared with those in the control group, and also found higher levels of antibodies to Prevotella intermedia, Prevotella melaninogenica and Bacteroides forsythus but not to Actinobacillus actinomycetemcomitans, in RA patients [35].

Similar to this study, Choi and coworkers found that there was a significant difference in the number of teeth in patients with RA and controls. In the analysis of CPD severity, the incidence of moderate and severe CPD was significantly higher in RA patients compared to the control group and found a positive correlation between ACPA with periodontal inflammation. It is recognized that CPD may be a potential source of citrullinated proteins that can induce ACPA in RA. In their study, they examined the prevalence and severity of CPD and related factors in Korean patients with RA by comparing them with a control group. Oral hygiene was assessed by plaque index (PI) and the severity of destruction was assessed by the main clinical parameters: bleeding on probing (BOP), probing pocket depth (PPD), clinical attachment level (CAL) as well as a gingival index (GI) for the evaluation of the inflammatory process [19].

The ability of the most common periodontal pathogen PG to express PPAD is a potential explanation for the thesis that chronic periodontal infection is a factor in the pathogenesis of RA. PPAD is indicated to citrullinate human fibrinogen and α-enolase by cross-reacting with human peptides. It is suggested that, through molecular mimicry alone, PG can induce antigenic peptides to be citrullinated by bacterial PPAD. It has been suggested that chronic exposure to citrullinated proteins in predisposed subjects with PD is able to generate autoantibodies and to stimulate the development of RA. An analogy is made with the thesis of impaired immune tolerance to citrullinated epitopes based on inflammatory pulmopathy in smokers [19].

Since citrullinated proteins are targeted for the production of auto-antibodies and PG possesses PPAD, it is reasonable to assume that protein citrullination is the mechanism by which PG participates in the development of RA [11,39].

Marchesan *et al*. in experimental models of collagen-induced arthritis in mice, concluded that chronic infection with PG triggers the activation of the immune system, favoring Th17 cellular responses and ultimately accelerating the development of arthritis. On this basis, they suggested that chronic oral infection may affect the development of RA mainly by activating Th17-related pathways [15]. Negative effects on articular inflammation have been reported to be exerted by PG through deregulation in Th17-IL-17A signaling in a model of collagen-induced arthritis, with no changes in ACPA responses.

Induction of innate immune responses in non-immune cells with PG has been reported. Incubation of *in vitro* human RA synovial fibroblasts with PG has been shown to increase the expression of TLRs, MMPs 1 and 3, as well as the production of IL-8 [39]. The increased risk of various diseases that PG is associated with is thought to be mediated, at least in part, by changes in their metabolic profiles.

As and coworkers consider that oral administration of PG may alter the composition of the intestinal microbiota, dysbiosis being associated with impaired intestinal barrier function leading to endotoxinemia, subsequent inflammation of the liver and adipose tissue, and worsening of collagen-induced arthritis through intestinal dysbiosis [40]. Increase of Th17 response in the intestine. PG has been shown to be able to exacerbate arthritis by causing intestinal barrier dysfunction [39].

The homeostatic role of n-3 docosapentaenoic acid (n-3 DPAwhich derived resolving - RvD5n-3 DPA), has recently been discovered in regulating the function of the intestinal epithelial barrier; decreased levels of this mediator during inflammatory arthritis are associated with increased permeability of the intestinal barrier and inflammation of the joints. Studies evaluating the mechanisms induced by PG to promote inflammation show that this bacterium regulates prostaglandins biosynthesis, leading to activation of innate cellular immunity [39].

PG is believed to be able to exacerbate arthritis by causing intestinal barrier dysfunction, the mechanism being demonstrated in murine models [39,41,42]. In mice with induced arthritis, there is impaired intestinal barrier function compared to naive mice, marked by down regulation of Tjp1 and Lyz1, as well as increased endotoxin plasma concentrations. Inoculation of arthritic mice with PG exacerbates those changes and results in increased bacterial loading in lamina propria and the intestinal mucosal layer compared with un-inoculated arthritic mice. The same bacterial changes

in the intestinal barrier were not observed in non-arthritic mice inoculated with PG [41].

It is hypothesized that the impact on the microbial communities involved in the disease mechanisms would also affect the diseases themselves provoked by them [4]. Some authors suggest that future research focused on the relationship and possible mechanisms of PG may be the basis for effective treatment and even prevention of RA, through effective treatment of CPD (conservative and / or surgical) maintaining a stable clinical condition in RA, without relapses [24].

According to Wolfe, rheumatologists should inform patients about the higher risk of CPD and should refer then directly to intensive dental care [43]. Kaur *et al*. also recommend that gingival tissue infections should be taken into account in the pathogenesis of RA and that chronic periodontal infections should be treated and prevented [44].

The appropriate recommendation in the case of severely impaired dentition of individual teeth or in severe CPD is to begin treatment of the teeth, the conventional therapy being mainly mechanical and expressed in scaling (cleaning) and periodontal root scraping for removal of plaque biofilm [8,13,19]. Monitoring is recommended after 1-3 months by evaluating probing pocket depth (PPD). The approach varies according to the severity of the changes, with mild forms preventative care is sufficient - regular brushing, regular monitoring by a dentist, smoking cessation recommended, while resection and grafting may be required in severe forms. Additional risk factors and concomitant systemic diseases correlating with an increased incidence of PD, as in RA patients, require recommended control every 1 to 3 months [19]. In order to reduce the depth of the pocket and optimize access, surgical treatment and the use of antibiotics and antimicrobials are sometimes also used [13]. In case of significant loss of tooth supporting tissues, surgical procedures are sometimes performed to restore the periodontal architecture and stimulate the regeneration of the supporting tissues. The benefits, however, of treating CPD come from reducing chronic inflammation and the risks associated with potential focus of infection in the oral cavity [8].

The administration of monoclonal antibodies directed to PG antigens is a potential method of immunotherapy. Most vaccines target one or more antigenic components of mono-infectious bacteria or viruses, although they are a multimicrobial biofilm. Most immunization approaches, both active and passive, against PD target a limited number of antigenic components of a specific pathogen. A combined strategy targeting both specific pathogenic species and the host immune response is recommended [18].

The established role and impact of CPD in the development and progression of a number of systemic diseases require a more comprehensive view of the therapeutic options for its response and control, including the development and administration of vaccines [18]. It is hypothesized that, in addition to the use of conventional therapy, the administration of the vaccine in patients with CPD would contribute to preventing dysbiosis and disease progression by preventing the recurrence of PG in the subgingival plaque. Vaccination targeting PG gingipains with the generation of gingipain neutralizing antibodies is proposed, followed by a less pronounced inflammatory Th2 response. Effects on CPD through vaccination would also have a beneficial effect on RA, as well as other diseases and complications for which oral infection is a risk factor [13]. Immunization with purified fimbriae has also been shown to provide protection against periodontal destruction in a model of gnotobiotic rat [17].

Following treatment of PG-inoculated arthritic mice, administration of RvD5n-3 DPA has been reported to restore intestinal barrier function, correcting host immune responses and reducing joint inflammation. Restoration of the function of the intestinal barrier after administration of RvD5n-3 DPA is accompanied by reduction of joint inflammation and swelling, reducing leukocyte infiltration in arthritic joints [39,41,42]. It is argued that new therapeutics based on RvD5n-3 DPA may also be potential therapeutic options in RA as they regulate both the intestinal barrier and the inflammation of the joints and it would be possible to develop customized therapeutic strategies after stratification of RA patients based on the presence of PD and elevated PG levels [41].

CONCLUSION

The oral periodontal pathogen PG, which has been identified as a major pathogen for CPD development, might have a role in the pathogenesis of RA. Despite discussions regarding the mediating mechanism, many studies agree on the view of its involvement in the development of RA. That is why treatment-preventive measures directed against PG should be considered in the treatment of RA. In addition to the conventional

therapy used for the treatment of RA, prevention of oral health is another option for influencing RA severity. This implies a collaborative approach in the follow-up of patients with RA in collaboration with a periodontitis, with local procedures for periodontal rehabilitation, treatment of CPD and eradication of PG added to the immunosuppressive treatment. Complex treatment combining more than one therapeutic approach may also guarantee a higher success rate for eradication of Porphyromonas gingivalis in RA patients which will lead to the improvement of their overall health and wellbeing.

ABBREVIATIONS

RA = Rheumatoid Arthritis

PD = Periodontal Disease

PG = Porphyromonas Gingivalis

Anti-CCP = Anti-Cyclic Citrullinated Protein/Peptide Antibodies

Anti-MCV = Anti-Modified Citrullinated Vimentin Antibodies

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Received on 16-09-2021 Accepted on 07-10-2021 Published on 27-10-2021

https://doi.org/10.12970/2310-9874.2021.09.01