CONCISE REPORT

Periodontal disease is significantly higher in non-smoking treatment-naive rheumatoid arthritis patients: results from a case-control study

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Accepted 3 May 2012

ABSTRACT

Objective To find the strength of association between periodontal disease (PD) and rheumatoid arthritis (RA) in non-smoking, disease modifying antirheumatic drug (DMARD)-naive RA patients in a case-control design.

Methods Patients of RA (DMARD-naive, non-smokers) satisfying the American college of Rheumatology 1987 criteria and healthy controls were included. PD was defined as present if the mean pocket depth (MPD) is ≥3 mm. Demographic data and disease specific variables were recorded for RA patients and healthy controls. Titres of immunoglobulin M-rheumatoid factor (IgM-RF) and anticitrullinated peptide antibodies (ACPAs) were measured using ELISA.

Results Patients with RA (n=91) had a 4.28 (CI 2.35 to 7.38) higher odds of PD (64.8% vs 28%, p<0.001) compared with healthy controls (n=93). The MPD was 3.61±1.22 mm in cases and 2.46±0.74 mm in controls (p<0.001). IgM-RF titres (110.56±95.81 vs 66.53±70.29; p=0.02) and ACPA titres (753.05±1088.27 vs 145.15±613.16, p=0.001) were significantly higher in RA patients with PD than those without PD. The MPD positively correlated with titres of ACPAs in RA patients (r=0.24; p=0.02).

Conclusions PD is more frequent and severe in non-smoking DMARD-naive RA patients compared with healthy controls. PD in RA is associated with high titres of ACPAs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting multiple synovial joints of unknown aetiology. Gene–environment interactions may play a potential role in the pathogenesis of this disease.[1] Tobacco smoking is one of the environmental factors strongly associated with RA and generation of anticitrullinated peptide antibodies (ACPAs) in the genetic background of positive human leucocyte antigen DRB1 shared epitope alleles.[2–4]

More recent data have suggested that periodontal disease (PD) could also be an environmental trigger in the pathogenesis of RA.[5–9] *Porphyromonas gingivalis* is one of the major oral pathogens causing periodontitis.[8] *P gingivalis* is the only pathogen known to express the enzyme, peptidyl arginine deiminase, which is capable of generating citrullinated peptides in periodontium.[5 9 10] Although the generation of citrullinated peptides is a normal physiological process involved in protein folding and degradation, immune responses generated against these citrullinated peptides are a unique feature in RA and predate the onset of disease by several years.[11 12] In such a chronic pro-inflammatory cytokine rich environment in periodontal pockets, it has been hypothesised that immune responses generated against these citrullinated peptides in genetically susceptible individuals may be a potential environmental trigger for RA. Studies demonstrated association of PD in patients with advanced RA who are already on disease modifying antirheumatic drugs (DMARDs).[5–7] There are no data to suggest this association in treatment-naive RA patients (not on any DMARDs). Smoking is also a strong risk factor for PD.[13 14] Therefore, tobacco smoking could be a potential confounding variable for the presence of PD in RA. With this background, we attempted to find the strength of association of PD in non-smoking DMARD-naive RA patients attending a rheumatology clinic at a university hospital in a case-control design. We also attempted to find the correlation of PD in these patients with disease activity titres of immunoglobulin M-rheumatoid factor (IgM-RF) and ACPAs.

PATIENTS AND METHODS

This study included 91 RA patients (adults>18 years, non-smoking, DMARD-naive satisfying the American college of Rheumatology 1987 criteria) and 93 age and sex matched healthy controls (non-smoking patient attenders, nursing staff and hospital technicians).[15] All participants gave written consent, and the study was approved by the Ethics Committee Board of the Nizam's Institute of Medical Sciences, Hyderabad, India.

Baseline demographic characteristics were recorded in all patients and healthy controls; disease specific variables were also included in RA patients, that is, duration of illness, early morning stiffness, tender and swollen joint counts (at 28 joints), joint deformities and patient global assessment of disease severity on a visual analogue scale. Disease activity was measured using disease activity score 28 (DAS 28)-erythrocyte sedimentation rate (ESR) four variables.[16]

PD assessment was done by a periodontist using a screening questionnaire for the presence of gingival

swelling, gingival bleeding, tooth sensitivity, tooth mobility and past history of tooth loss due to PD (excluding other causes of tooth loss due to endodontic infection, fracture or trauma based on history alone). The pocket depths were measured using Williams graduated periodontal probe for each tooth at six surfaces (mesiobuccal, midfacial, distobuccal, mesiolingual, mid-lingual and distolingual surfaces). The mean pocket depth (MPD) was calculated by adding the pocket depths of individual teeth and dividing it by the number of sites examined. PD was present if the MPD is ≥3 mm.[17 18]

Blood samples from RA patients were analysed for titres of IgM-RF by ELISA using kits from Wampole laboratories (New Jersey, USA) and ACPAs using second generation ELISA kits from Euro Diagnostica (Malmo, Sweden). The cut-off positive values taken for IgM-RF and ACPAs were >40 IU/ml and >25 U/ml, respectively.

Statistical analysis

Associations are given in terms of OR or Spearman's ρ correlation. Proportions are compared using Pearson's χ^2 test, means are compared using Student's t test and highly skewed distributions are compared using Wilcoxin–Mann–Whitney's test. Data are reported as mean±SD unless otherwise stated, and 95% CI are reported where relevant. Two-sided p<0.05 were considered significant. The data were entered and analysed using statistical software SPSS V.17.

RESULTS

PD was present in 64.83% (59/91) of RA patients and in 28% of healthy controls (26/93). PD was significantly higher in RA patients compared with healthy controls (p<0.001). Patients with RA had a 4.28 (CI 2.35 to 7.80) higher odds of having PD compared with healthy controls. The MPD was 3.61±1.22 mm in RA and 2.46±0.74 mm in healthy controls and this was statistically significant (p<0.001) (further demographic details are mentioned in table 1).

The MPD were significantly higher in RA with ACPA positive patients compared with RA with ACPA negative patients (3.94±1.13 mm vs 3.40±1.25 mm; p=0.04). However, both the groups had significantly higher MPD compared with healthy controls (2.46±0.74 mm) (see online supplementary figure S1). But, the MPD was not significantly different among IgM-RF positive and negative patients (3.58±1.10 mm vs 3.65±1.40 mm; p=0.8); however, both the groups had significantly higher MPD compared with healthy controls (see online supplementary figure S2). RA patients were also analysed based on the presence or absence of ACPA positivity (table 2); RA with ACPA positivity was associated with longer duration of the disease (median of 12 (3–120) vs 5 (2–60) months; p=0.001), more pronounced elevation of ESR (52.56±19.69 vs 41.57±20.44 mm in the first hour; p=0.01) and higher DAS 28 (7.21±0.72 vs 6.79±0.79; p=0.01) compared with RA with ACPA negative.

In a subgroup analysis of RA with PD and without PD, the PD group had DAS 28 score of 7.08±0.77 and RA without PD had 6.81±0.82 (p=0.12). The PD group had slightly higher disease activity; however, this was not statistically significant (table 3). The mean age, duration of illness, duration of early morning stiffness, tender joint count, swollen joint count, patient global assessment and ESR were not different among the groups (table 3).

IgM-RF was positive in 57 patients (63%) and titres were significantly higher in the PD group (110.56±95.81 vs 66.53±70.29 IU/ml; p=0.02) than those without PD (table 3). ACPAs were positive in 36 patients (done in 89 patients; 41%); of them 32 were positive in the PD group while only four patients in those without PD (table 3). Further, the ACPA titres were significantly higher in the PD group (753.05±1088.27 vs 145.15±613.16 IU/ml; p=0.001) (see online supplementary figure S3). The MPD correlated positively with titres of ACPA (r=0.24; p=0.02); however, there was no correlation with IgM-RF (r=0.12; p=0.25).

Table 1 Demographic variables and PD in RA patients and healthy controls

Variables	RA patients	Controls	p Value
Number of patients	91	93	NA
Age distribution (years)	43.92±11.38	41.75±11.04	0.19
Sex (M:F)	15:76	24:69	0.18
PD	59 (64.83%)	26 (28%)	<0.001
Tooth loss (due to PD)	10	0	0.001
Mean pocket depth (mm)	3.61±1.22	2.46±0.74	<0.001

NA, not applicable; PD, periodontal disease; RA, rheumatoid arthritis.

Table 2 Demographics, disease activity and autoantibody titres in rheumatoid arthritis patients based on ACPA positive or negative. Tender and swollen joints were based on 28 joint counts. The data were expressed in mean±SD, median (IQR), and percentages

Variable	ACPA positive (n=36)	ACPA negative (n=53)	p Value (two-tailed)
Age (years)	42.42±11	44.83±11.29	0.32
Sex (F:M)	32:4	42:11	0.23
Duration of illness (months)	25.14±32.15; 12 (3–120)	8.7±12.52; 5 (2–60)	<0.001
EMS (min)	107.50±31.57	79.25±33.84	<0.001
TJC	22.50±5.25	21.58±6.17	0.47
SJC	12.08±7.59	10±5.45	0.14
PGA	66.75±19.15	62.04±19.68	0.27
ESR	52.56±19.69	41.57±20.44	0.01
DAS 28-ESR	7.21±0.72	6.79±0.79	0.01
RF (IU/ml)	172.64±77.72; 198 (2–288)	42.64±51.40; 36 (1–274)	<0.001
ACPA (IU/ml)	1334.25±1174; 1030 (30–3704)	2.70±4.2; 1 (1–20)	<0.001
MPD (mm)	3.94±1.13	3.41±1.25	0.04
Periodontal disease	33 (91.67%)	26 (49.05%)	<0.001

ACPA, anticitrullinated peptide antibody; DAS 28, 28-joint disease activity score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; MPD, mean pocket depth; PGA, patient global assessment; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

Table 3 Demographics, disease activity and autoantibody titres in rheumatoid arthritis patients with PD versus without PD. PD was present if the mean pocket depths is ≥3 mm. Tender and swollen joints were based on 28 joint counts. The data were expressed in mean±SD, median (IQR) and percentages

Data	PD present (n=59)	PD absent (n=32)	p Value
Age (years)	45.08±10.23	41.78±13.13	0.19
Sex (F:M)	49:10	27:5	0.87
Duration (months)	17.14±26.28; 6 (2–120)	12.91±18.68; 4 (2–72)	0.2
EMS (minutes)	91.53±37.55	90.94±31.86	0.94
TJC	22.19±5.81	21.84±5.84	0.78
SJC	11.63±6.52	9.47±6.00	0.12
PGA	66.22±18.78	61.44±21.28	0.27
ESR	48.36±21.98	42.81±17.84	0.22
DAS 28-ESR	7.08±0.77	6.81±0.82	0.12
IgM-RF positivity (63%) (57/91)	66.1% (39/59)	56.3% (18 /32)	0.35
ACPA positivity (41%) (36/89)	55% (32/58)	13% (4/31)	< 0.001
IgM-RF titres (IU/ml)	110.56±95.81; 95 (2–288)	66.53±70.29; 51 (1–222)	0.02
ACPA titres (IU/ml)	753.05±1088.27; 51 (1–3704)	145.15±613.16; 1 (1–3360)	0.001

ACPA, anticitrullinated peptide antibody; DAS 28, 28-joint, disease activity score; EMS, early morning stiffness; ESR, erythrocyte sedimentation rate; IgM, immunoglobulin M; PD, periodontal disease; PGA, patient global assessment; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

Patients with RA were further analysed for PD symptoms, gingival swelling was noted in 48 RA patients with PD (n=59) and in 14 patients without PD (n=32) (OR=5.6 (CI 2.2 to 14.6); p<0.001); gingival bleeding in 58 RA patients with PD and in 28 patients without PD (OR=8.3 (CI 0.9 to 77.6); p=0.03); tooth sensitivity in 50 RA patients with PD and 22 patients without PD (OR=2.5 (CI 0.9 to 7.1); p=0.07); however, tooth mobility (15/59, p=0.002) and tooth loss due to PD (10/59, p=0.01) were noted only in the PD group.

DISCUSSION

We demonstrated that PD is more frequent and severe in non-smoking DMARD-naive RA patients who are more likely to be edentulous due to PD than healthy controls. The titres of ACPA and IgM-RF are significantly higher in RA with PD. This association is much stronger for ACPA than IgM-RF. We also find that pocket depths in RA patients positively correlated with the titres of ACPA and not for IgM-RF. In a cross-sectional survey of non-institutionalised population in the USA (NHANES III survey), participants with RA were more likely to have periodontitis with an OR of 1.82 (CI 1.04 to 3.20) and these patients are more likely to be edentulous than the healthy population.[6] In another case-control study from Germany, subjects with RA had an 8.05 increased odds of PD compared with controls (CI 2.93 to 22.09) and on logistic regression analysis, RA and age remained significant predictors of PD.[5] It was demonstrated that IgG levels of *P gingivalis*, *Prevotella intermedia*, *Prevotella melaninogenica* and *Bacteriodes forsythus* (predominant oral pathogens) are significantly higher in sera of patients with RA compared with controls.[9] Further in a study involving North American Native population, it is well demonstrated that in a genetically predisposed individuals with RA and their relatives, anti-*P gingivalis* antibodies were associated with ACPAs and further immune responses to *P gingivalis* may be involved in breaking immune tolerance to citrullinated antigens.[7] Previous studies were carried out in patients with established RA; this study analysed the frequency of PD in DMARD-naive RA. It is possible that in long standing RA, the presence of cofounding variables like poor hand grip, elbow, shoulder function and difficulty in maintaining oral hygiene may predispose patients to PD over a period of time. Similarly, anti-inflammatory therapy may ameliorate surrounding inflammation in periodontitis.[19–22] This study shows a higher frequency of PD in non-smoking DMARD-naive RA and further strengthens this association.

In a pilot study, we found the titres of ACPA were significantly higher in gingival crevicular fluid compared with serum in RA with PD (unpublished data). In some RA patients with PD, a negative result for ACPA in serum was found to be positive for ACPA in gingival crevicular fluid (unpublished data). Studies has clearly shown that the ACPA positivity in RA increases with duration of the disease from 41% (<3 months of disease) to 64% (<12 months of disease).[23 24] In the present study, we demonstrated that treatment-naive RA patients with ACPA positivity are associated with a longer duration of the disease compared with those without ACPA positivity. It is possible that such untreated PD in RA patients may account for further ACPA positivity in serum at the later part of the disease. Studies are needed to further explore this hypothesis.

Strong evidence already exists to support the role of tobacco smoking as a potential environmental risk factor in the pathogenesis of RA and also PD.[2–4] The high odds of presence of PD in non-smoking RA patients demonstrates the consistency of its association. It is also possible that smoking potentiates RA through PD. It is also hypothesised that PD maintains systemic inflammation by continuous generation of citrullinated peptides in periodontal pockets.[25] In this study, a slightly higher disease activity was noted in RA with PD; however, this is not statistically significant. Studies has shown that presence of ACPA is associated with severe RA.[26] It could be expected that patients with PD may have severe RA and may tend to be more DMARD-resistant. However, further follow-up studies are essential to support this hypothesis and also the role of treatment of periodontitis in RA patients on disease activity.

Our study concludes that PD is more common and severe in RA patients than healthy controls. PD is strongly associated with the presence of ACPAs and could be a potential environmental trigger in the pathogenesis and also in the maintenance of systemic inflammation in RA. Further large scale prospective studies are needed to confirm this potential association.

Acknowledgements The authors acknowledge the Indian council of medical research (ICMR) for granting partial financial support as part of DM thesis grant to the first author.

Contributors DP designed the study, and was actively involved in the collection and interpretation of the data, and manuscript draft preparation, KCD and SP were

actively involved in the periodontal examination of rheumatoid arthritis patients and manuscript drafting. NG SA, LR and SK were involved in manuscript drafting, critical revision and statistical support and AK in laboratory support and manuscript drafting. All the authors revised and approved the final revised manuscript for submission.

Funding Indian Council of Medical Research (ICMR).

Competing interests None.

Patient consent Obtained.

Ethics approval Approval provide by the Ethical committee Board of the Nizam's Institute of Medical Sciences.

Provenance and peer review Not commissioned; externally peer reviewed.

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Ann Rheum Dis 2012 71: 1541-1544
doi: 10.1136/annrheumdis-2011-200380