An observation on the severity of periodontal disease in past cigarette smokers suffering from rheumatoid arthritis- evidence for a long-term effect of cigarette smoke exposure?

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Abstract

Background: Rheumatoid arthritis (RA) and cigarette smoking are both risk factors for periodontal disease (PD). Previous research suggests that systemic inflammatory conditions and cigarette smoking may act in synergy, and their co-occurrence leads to a much higher risk of developing severe stage PD than what the combination of their individual risks would suggest. We originally sought to test this in the case of RA, but it turned out that the majority of our patients were former smokers, who smoked for prolonged periods in the past. For that reason, we decided to shift our focus toward the possible effects of past chronic cigarette smoke exposure.

Methods: The data of 73 RA patients and 77 healthy controls were analyzed. The participants received a full-mouth periodontal examination to determine their periodontal status. Rheumatological indices and data on past tobacco use were also recorded. Both the patient and the control groups were divided into former smoker and non-smoker subgroups for the analyses. Non-smoker controls were used as the reference group.

Results: In the control group, smoking in history increased the odds of developing both the moderate and the severe stages of PD, but the change was not statistically significant. RA significantly, increased the odds of developing both stages in itself, but the highest odds were seen in the former smoker RA group.

Conclusion: Based on this surprising observation of ours, we hypothesize that chronic cigarette smoke might bring about permanent changes in the periodontal tissues, leading to their hypersensitivity to inflammatory challenges.

Keywords: Rheumatoid arthritis, Periodontal disease, Chronic inflammation, Late sequelae, Tobacco smoking

Background

The connection between periodontal disease (PD) and various systemic conditions of an autoimmune/dysimmune background is well documented [1–5]. Rheumatoid arthritis (RA) is an immune mediated disease with a particularly well established link to PD [6–9]. While the exact immunological mechanisms have not been clarified, there is evidence to suggest that the presence of citrullinated proteins (and antibodies against them) is the link [10–12].

In this respect, the role of the periodontal pathogen, Porphyromonas gingivalis is emphasized, the only periodontal pathogen that expresses the citrullinating enzyme peptidyl-arginine deiminase (PPAD) [9, 13, 14]. Compared to the general population, subjects with PD are at an increased risk of developing RA, and vice versa [9, 15], which suggests that once they are established, they mutually aggravate each other.

Cigarette smoking is a known risk factor for both PD [16–18] and RA [19–21]. Cigarette smoking promotes oral bacterial colonization [22] and smoking itself has been shown to promote citrullination [23], evidenced by the fact that an association was found between tobacco...
exposure and anti-cyclic citrullinated peptide (anti-
CCP) titers in RA patients [24]. It follows that
cigarette smoking may be an additional aggravating
factor in both PD and RA, especially when the two
conditions are comorbid.

In 2014, we published a study about the effects of
cigarette smoking on the severity of PD in psoriasis [25].
In that study, we found that while both psoriasis and
smoking significantly elevated the odds that the individ-
ual will develop advanced PD, when both risk factors
were present, the odds multiplied, well beyond the com-
bined odds. We concluded that cigarette smoking prob-
abley acted as a permissive factor, and we articulated a
hypothesis about the possible role of toll-like receptor 4
(TLR-4). The hypothesis was that smoking exerts this ef-
fect through the upregulation of TLR-4.

In their review [26], Baka and co-workers point out
that as cigarette smoking promotes bacterial colonization,
it may well be that smokers are exposed to an increased
burden of P. gingivalis, whereby they are constantly ex-
oposed to a potent antigen.

Based on these premises, we wished to find out about
if smoking acts as a booster of periodontal deteriora-
tion also in the context of RA. This is an important question
with practical bearings. For instance, severe PD was
reported to hamper the efficacy of anti-TNF (tumor ne-
crosis factor) therapy [27].

To answer the question, we collected data on 82 RA
patients and 100 controls who met all the inclusion and
exclusion criteria and also gave their informed consent.
At this point, though, we were faced with a difficulty:
most of our patients turned out to be non-smokers
(NS). Only eight of them smoked at the time of the study,
and the rest had either quit or never ever smoked
in their lives. The majority of our patient sample, there-
fore, consisted of non-smokers and former smokers (FS)
who had quit smoking long before.

While we have a wealth of information about the im-
munological consequences of current smoking [28–31],
we know almost nothing about the permanent immuno-
logical changes that chronic exposure to cigarette smoke
may bring about - and that may remain even if the smoker
quits. Considering that the majority of our formerly smok-
ing patients had smoked for at least a decade before they
quit, and that chronic exposure to cigarette smoke was
proven to induce genome level changes [32–34], we
decided to shift our focus and concentrate on the effects
of past smoking. We hypothesized that the periodontal
status of patients with no smoking history would be sig-
ificantly poorer than that of healthy controls (the effect
of RA), and we wished to know if past smoking would be
associated with poorer periodontal status to any extent.
We were also interested in the relationship between the
rheumatological factors and the periodontal status.

Methods
Both RA patients and healthy controls were recruited on
a voluntary basis.

Patients were eligible for the study if they met the
2010 European League against Rheumatism and
American College of Rheumatology (EULAR/ACR)
criteria for rheumatoid arthritis [35]. Exclusion
criteria for both groups were determined based on
the literature of the subject and included obesity
(body mass index - BMI ≥ 30), excessive alcohol con-
sumption, drug abuse, diabetes mellitus, diseases causing
neutropenia and local or systemic inflammatory condi-
tions (other than RA) [36]. Poor oral hygiene, defined as
Simplified Oral Health Index (OHI-S) > 3 [37] was also
an exclusion criterion.

Required sample size was calculated with G*Power 3.1.5.
(University of Kiel, Germany), a software designed
especially for statistical power and sample size computa-
tion [38]. The software allows the computation of
achieved statistical power (post-hoc) and required sam-
ple size (a priori). As mostly categorical variables were
to be analyzed, a priori sample size estimation was per-
formed for crosstabs/chi square/contingency tables, with
the following input parameters: effect size (ω): 0.3; α: 0.05;
power (1-β): 0.9; df: 3. Required sample size turned
out to be n=158 (for four groups: RA smoker/former
smoker; control smoker/former smoker).

RA Patients (n = 82) were recruited from among the
patients of the Department of Rheumatology, University
of Szeged. The control group (n = 100) was recruited
from among people attending mandatory lung screening
in the same city and the same period. After removing
the actual smokers from the sample, we were left with
150 participants (73 patients and 77 controls), yielding a
statistical power of 0.88.

The study was approved by the Institutional and Re-
ional Ethics Committee for Medical Biological Research
at the University of Szeged (approval No.144/2014), and
the study design conformed to the Declaration of
Helsinki in all respects. Written informed consent was
obtained from all participants.

Demographic and tobacco use data were collected by a
questionnaire. Participants were divided into FS and
non-smoker groups, based on their self-reported tobacco
use in the past. In both the patient and the control
groups, a subject was considered a FS if they smoked for
at least one year in the past as a habit and without inter-
ruption. Sixty-four percent of the FS controls and 74 %
of the FS RA patients provided tobacco use information
that could be used for the analyses.

The clinical disease severity of PD is still a matter of
debate, and several methods are available in the litera-
ture [39]. We decided to use the staging proposed by
Fernandes and colleagues [40]. The reason for using this
classification was that its clinical staging matches the pathological/pathophysiological changes in PD very well [41], and that we had had previous experience with it [25]. The staging requires the following parameters to be recorded: bleeding on probing (BOP; the presence or absence of bleeding within 15 s after probing), probing depth (PRD; in millimeters), and clinical attachment level (CAL; to describe the position of the soft tissue in relation to the cemento-enamel junction). All subjects received a full-mouth examination and their periodontal status was classified into one of the four categories of the staging: healthy(0); early (1); moderate (2); severe (3). For the examination, Williams probes (Hu-Friedy Manufacturing Co., Chicago, USA) were used. Table 1 shows the categories of the applied staging and the corresponding pathological/pathophysiological status.

Table 1 The applied clinical staging and the corresponding pathological/pathophysiological changes [40, 41]

| CLINICAL STAGING (Fernandes et al., 2009) | PATHOLOGY/PATHOPHYSIOLOGY (Ohlrich et al., 2009) |
|------------------------------------------|--------------------------------------------------|
| 1. NO CLINICAL SIGNS - no clinical attachment loss (CAL) or bleeding on probing (BOP) | NO LESION - NOT CLASSIFIED EXPLICITLY IN OHLRICH ET AL. |
| (GINGIVITIS-NOT CLASSIFIED EXPLICITLY IN FERNANDES ET AL.) | 1. INITIAL LESION – up to 4 days following plaque accumulation. Polymorphonuclear leukocytes (PMNs), complement activation, loss of connective tissue. Mast cells release tumor necrosis factor alpha, PMNs migrate into the gingival sulcus, but as the bacteria are protected by the biofilm, abortive phagocytosis occurs. PMNs release lysosomal contents, which leads to further tissue destruction. |
| 2. EARLY PERIODONTITIS - CAL ≥1 mm in ≥2 teeth | 2. EARLY/STABLE LESION - 7-21 days after plaque accumulation, clinically evident approximately from day 12. Dominantly macrophages and lymphocytes (CD4+CD8- 2:1). Perivascular inflammatory infiltrate. Intercellular spaces between epithelial cells widen, bacterial products infiltrate the gingival tissues at a higher rate. Escalation of response. If plaque removed, tissue remodeling can take place. |
| 3. MODERATE PERIODONTITIS - 3 sites with CAL ≥4 mm and at least 2 sites with probing depth (PRD) ≥3 mm | 3. ESTABLISHED OR PROGRESSIVE LESION - dominantly a B cell/plasma cell response. High levels of IL-1 and IL-6: connective tissue loss, breakdown of bone. |
| 4. SEVERE PERIODONTITIS - CAL ≥6 mm in ≥2 teeth and PRD ≥5 mm in ≥1 site | 4. ADVANCED LESION - Overt loss of attachment. High levels of IL-1, TNF α and PGE2 stimulate fibroblasts and macrophages to produce matrix metalloproteinases. The junctional epithelium progresses in apical direction (deepening periodontal pocket). Oligoclonal Th2 (CD4+) dominance. |

To characterize the patient population from a rheumatological point of view, the following indices and laboratory values were recorded: IgM rheumatoid factor seropositivity and levels (RF) measured with nephelometry, anti-citrullinated peptide antibody (ACPA) seropositivity and levels with antigenic specificity to mutated citrullinated vimentin (aMCV) measured with ELISA, disease activity score (DAS28-ESR) at the latest visit and its average of the past 12 months, and the HAQ-DI disability index. Data on the conventional and biological disease modifying anti-rheumatic drug (DMARD) and corticosteroid therapy of the patients were also recorded. Laboratory values were determined as part of the routine examinations (i.e. not especially for this study).

We divided the subjects into four groups based on the presence/absence of RA and smoking in the past. To express the odds that a member of a given group develops a given clinical degree of periodontal disease, multinomial logistic regression analysis was conducted and the odds ratios were calculated. In the multinomial

Table 2 Demographic and tobacco use characteristics of the studied groups

| Group | Sex ratio F(%):M(%) | Smoke-free for (mean years, SD) | Smoked for (mean years, SD) | Cigarettes smoked per day (rounded average, SD) | Age in years (mean, SD) |
|-------|--------------------|--------------------------------|----------------------------|-----------------------------------------------|------------------------|
| CNS (n = 55) | 44(80):11(20) | NA | NA | NA | 55.7 (13.3) |
| CS (n = 22) | 12(54):10 (45) | 11.3(12.5) | 13.8(10.2) | 11 (7.9) | 58.1 (13.5) |
| PNS (n = 42) | 33(79):9 (21) | NA | NA | NA | 58.65 (12.7) |
| PS (n = 31) | 24(77):7 (23) | 16.4(12.2) | 18.3(11.4) | 14 (10.2) | 59.3 (13.6) |

CNS control, never smoked, CS control, used to smoke, PNS patient, never smoked, PS patient, used to smoke
model, disease severity (healthy, early, moderate, severe) was defined as the outcome variable, group was the factor, and age and sex were covariates. Within-group analyses (Mann-Whitney U tests) were also performed in the patient group, according to the smoking status, to see if past smoking had any effect on the rheumatological indices. For the analyses, SPSS 21.0 (IBM, USA) was used.

**Results**

The demographic and tobacco use characteristics of the four studied groups are given in Table 2. It can be seen that the vast majority of the participants were females. This is because RA affects predominantly women and the control group was selected to match the patient group age- and gender-wise as closely as possible.

The within-group comparisons in the patient group did not indicate significant difference in any of the rheumatological indices between FS and non-smokers (data not shown). To test the effect of RF/aMCV positivity on periodontal status, a separate multinomial regression analysis was conducted. While no statistically significant effects were found, seropositivity for RF increased the odds of the moderate stage to 1.65, and that of the severe stage to 2.51. The rheumatological indices of the patient group are summarized in Table 3.

The periodontal status and CAL data of each group is shown in Table 4. It is noteworthy that while the majority of the cases in both control groups falls into the healthy and early stages, in the patient groups the situation is just the opposite. This tendency is the most remarkable among the patients who used to smoke. 81% of them were classified as having moderate or severe PD. Note also that in the patient groups nobody was found who could be classified as periodontally healthy.

The results of the multinomial regression analysis are given in Table 5. The analysis indicated no significant influence of either age or sex on periodontal status. Male

| Table 3 | A brief rheumatological characterization of the patient population by smoking in patient history |
|---------|------------------------------------------------------------------------------------------|
| Rheumatoid factor positivity (>[30 U/ml] n (%) FS | 20 (64.5) |
| Anti-citrullinated peptide antibody positivity (>[20 U/ml] n(%) FS | 20 (64.5) |
| Patients on conventional DMARD therapy n (%) FS | 25 (80.6) |
| Patients on biological DMARD therapy (%) FS | 17 (54.8) |
| DAS28 at visit mean (SD; range) FS | (n=21) 3.10 (1.42; 0.97–6.52) |
| Average DAS28 in the previous 12 months mean (SD; range) FS | (n=10) 2.0 (1.68; 1.38–5.22) |
| HAQ mean (SD) FS | (n=15) 0.98 (0.84) |

FS former smoker, NS never smoked, DMARD disease-modifying antirheumatic drug, DAS28 disease activity score, HAQ score on the health assessment questionnaire for rheumatoid arthritis. Where data from not all patients were available, the actual number of patients is given in parentheses.

| Table 4 | Periodontal status in the examined groups according to Fernandes et al. (38). Data are given as n (%), rounded percentages. CAL values are also shown (mm, mean ± SD). The conventions are the same as in Table 1. |
|---------|------------------------------------------------------------------------------------------|
| RA          | Control |
| n          | CAL      | n          | CAL       |
| Total 73   | 3.55 (±1.62) | 77         | 2.03 (±1.17) |
| PNS         | PS       | CNS        | C5        |
| n          | CAL      | n          | CAL       | n          | CAL       | n          | CAL    |
| Total 42   | 3.18 (±1.39) | 31         | 4.06 (±1.79) | 55         | 2.08 (±1.26) | 22         | 1.91 (±0.89) |
| Healthy 0   | NA       | 0          | NA        | 8 (15)     | 0.67 (±0.30) | 4 (18)     | 0.76 (±0.40) |
| Early 12 (29) | 1.81 (±0.21) | 6 (19)     | 1.89 (±0.31) | 30 (55)    | 1.52 (±0.39) | 12 (55)    | 1.76 (±0.37) |
| Moderate 22 (52) | 3.07 (±0.32) | 12 (39)    | 3.50 (±0.89) | 13 (24)    | 3.35 (±0.21) | 5 (23)     | 3.19 (±0.25) |
| Severe 8 (19) | 5.52 (±1.21) | 13 (42)    | 5.57 (±1.46) | 4 (7)      | 4.99 (±0.14) | 1 (5)      | 4.72 (±NA)  |
sex appears to be associated with an increased risk for both the moderate and the severe stages, but given the under-representation of the male sex in this study, we would not draw conclusions from this. As for the odds of developing the moderate or severe stages, these were significantly higher in both patient groups for both stages as compared to controls who never smoked. Controls who used to smoke did not have significantly higher odds to develop any of these stages than controls who never smoked, while an increment was definitely seen. The highest significant odds ratio for the severe stage (16.25) was found in the RA group of FS.

Discussion
A part of these findings is merely the corroboration of known facts. RA has been known as a risk factor for PD for some time [6–8], and our results demonstrate the same: the presence of RA in itself is enough to significantly increase the odds that the patient will develop a more severe stage of PD.

We also found that past smoking did not have a significant effect on any of the rheumatological indices and that there was no association between these indices and periodontal status. The lack of the effect of past smoking on the rheumatological status as expressed by these indices might be best explained by the time passed since the patient stopped smoking. While cigarette smoke must have been an extra immunological stimulus while the patient was still smoking, and it might as well have boosted the immunological memory against citrullinated proteins [42], these effects are unlikely to be reflected in indices characterizing a much narrower time window.

How come that no association was found between the specific RA indices and the periodontal status, while, as pointed out before, being in the RA group in itself significantly increased the odds of the more severe PD stages? Given that other studies describing larger populations found significant association with rheumatoid factor positivity and anti-citrullinated peptide antibody production [43, 44], we think that our sample size was probably too small to allow reliable assessment at the level of the individual indices, considering their greater variability.

The main finding of this study, however, is also the most difficult to explain. The finding that the FS RA patients had the highest and significant odds ratio for the severe stage of PD is really an unexpected one. From the results it appears that the effect is not mediated by the actual rheumatological status, the presence of RA with a longer period of cigarette smoke exposure in the past is enough. This suggests that long-term cigarette smoking might permanently sensitize the periodontium, but at this point we could only speculate about the possible mechanisms, and it is because of that reason that we put this up for debate.

Conclusions
While this study definitely has its limitations, we think that our quasi-accidental finding about the effect of past smoking on periodontal health in RA deserves attention. This finding implies that long-term exposure to cigarette smoke might have a permanent sensitizing effect on the human periodontal tissues, which is not reversible by quitting smoking.

Abbreviations
ACP: Anti-citrullinated peptide antibody; aMCV: Mutated citrullinated vimentin; anti-CCP: Anti-cyclic citrullinated peptide; anti-TNF: Anti-tumor necrosis factor; BMI: Body mass index; BOP: Bleeding on probing;

### Table 5 Results of the multinomial regression analysis. The odds ratios (Exp(B)) express the odds that a member of the given group develops the given stage of periodontal disease. Controls who never smoked and early stage periodontal disease served as reference (as no periodontally healthy individuals were found in the patient group, healthy could not be used as reference). B: correlation coefficient; df: degrees of freedom

| Periodontal status (reference: early) | B     | df | Sig.  | Exp(B)    | 95% CI for Exp(B) |
|--------------------------------------|-------|----|-------|-----------|-------------------|
| moderate                             | RA- used to smoke | 1.529 | 1 | 0.011 | 4.615 | 1.423–14.966 |
| moderate                             | RA- never smoked | 1.442 | 1 | 0.003 | 4.231 | 1.623–11.030 |
| moderate                             | Control- used to smoke | 0.932 | 1 | 0.090 | 2.538 | 0.866–7.442 |
| moderate                             | Control-never smoked | – | – | – | – | – |
| moderate                             | Male sex | 0.223 | 1 | 0.643 | 1.250 | 0.487–3.212 |
| moderate                             | Age | 0.002 | 1 | 0.896 | 1.002 | – |
| severe                               | RA- used to smoke | 2.788 | 1 | 0.000 | 16.250 | 3.917–67.412 |
| severe                               | RA- never smoked | 1.609 | 1 | 0.022 | 5.000 | 1.265–19.762 |
| severe                               | Control- used to smoke | 0.405 | 1 | 0.666 | 1.500 | 0.238–9.465 |
| severe                               | Control-never smoked | – | – | – | – | – |
| severe                               | Male sex | 0.839 | 1 | 0.867 | 2.315 | 0.703–7.619 |
| severe                               | Age | 0.028 | 1 | 0.176 | 1.029 | 0.972–1.033 |
Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
MA organized the study; MA and EB performed the periodontal examinations and recorded patient data; MB and LK performed the rheumatological examinations and recorded patient data; GB performed the data analysis; EB, MB, LK, MA and GB prepared the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate
The study was approved by the Institutional and Regional Ethics Committee for Medical Biological Research at the University of Szeged (approval No.144/2014), and the study design conformed to the Declaration of Helsinki in all respects. Written informed consent was obtained from all participants.

Competing interests
The authors declare that they have no competing interests.

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