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LOW-GRADE SYSTEMIC INFLAMMATION MAY INCREASE THE RISK OF PERIODONTITIS

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SUMMARY

Subjects—The study participants for this analysis belonged to a prospective cohort from northeast Germany, the Study of Health in Pomerania. Data were collected from 1997 to 2001 for baseline measures and from 2008 to 2012 for follow-up. All participants were Caucasian, and 47% were male. The final sample size varied by the completeness of exposure and outcome information. The sample sizes for evaluating white blood cell (WBC) counts as the exposure in relation to probing depth (PD), clinical attachment loss (CAL), and the CDC/American Academy of Periodontology (AAP) case definition were 1784, 1697, and 1638, respectively. Likewise for fibrinogen level as the exposure, the sample sizes were 1764, 1680, and 1621, respectively.

Key Risk/Study Factor—The key risk factors in this study were systemic inflammatory markers, which were measured as WBC counts and fibrinogen. Both WBC and fibrinogen were collected from the nonfasting blood samples of the participants.

Main Outcome Measure—The main outcome measure was severity of periodontitis, which was assessed by PD, CAL, and the CDC/AAP case definition. PD and CAL were assessed at 4 sites per tooth. PD represents the distances from the gingival margin, and CAL represents the cemento-enamel junction to the bottom of the periodontal pocket. Only teeth remaining at follow-up were used during analysis. In the analysis, the variables were the mean values of PD and CAL and percentage of sites (extent) with PD or CAL ≥ 3 mm. The CDC/AAP case definition of periodontitis was a dichotomous measure: having at least 2 sites with PD ≥ 5 mm or CAL ≥ 6 mm. An alternative measure for the CDC/AAP case definition was the number of missing teeth, excluding third molars, and the percentage of decayed and filled surfaces based on half-mouth assessments.

Main Results—In this study, inflammatory markers at baseline were positively related to measures of periodontitis over the 11-year follow-up period. In the fully adjusted models, a 1 g/L-higher fibrinogen level was associated with an increase of 0.08 mm (0.05–0.11 mm) in mean PD and 0.10 mm (0.05–0.15 mm) in mean CAL. For a 1 Gpt/L higher WBC level, there was a mean increase of 0.01 mm (0.02–0.04 mm) in mean PD and 0.05 mm (0.03–0.08 mm) in CAL.

SORT SCORE NA

LEVEL OF EVIDENCE 2

To evaluate the extent to which low-grade systemic inflammation increased periodontitis risk

ARTICLE TITLE AND BIBLIOGRAPHIC INFORMATION

Longitudinal effects of systemic inflammation markers on periodontitis. Pink C, Kocher T, Meisel P, Dörr M, Markus MRP, Jablonowski L, Grotevendt A, Nauck M, Holtfreter B. *J Clin Periodontol* 2015;42(11):988–97.

Similarly, for the extent measure, a 1-unit higher fibrinogen level corresponded to an increase of approximately 3% in PD and CAL and 1% increase in PD and CAL for 1 unit higher in the WBC level. Fibrinogen and WBC were also positively associated with the CDC/AAP case definition but not with the number of missing teeth or percentage of decayed and filled surfaces.

Conclusions—The authors concluded that systemic inflammation at baseline predicted periodontal destruction and clinical periodontitis at follow-up in a prospective study.

COMMENTARY AND ANALYSIS

Inflammation has been hypothesized to cause periodontal destruction based on findings from many smaller, mostly cross-sectional studies.¹ Pink et al.² found that higher levels of inflammatory markers at baseline were associated with more severe and extensive periodontal destruction and increased periodontitis development during 11 years of follow-up. The inflammatory markers were not related to tooth loss or carious or restored surfaces over the same period. The strengths of this study were its prospective design, large sample size, accurate measurements of exposure, good agreement between dental examiners, multilevel methods to control for correlated observations, adjustment for a number of potential confounders including obesity, and sensitivity analyses that were conducted.

However, the study had some shortcomings. First, of the 4308 individuals who were examined at baseline, 2333 were contacted at follow-up, and after exclusions, data from 1621 to 1784 individuals were analyzed in this report. Loss to follow-up causes selection bias in cohort studies when the reason for absence is related to exposure and outcome.³ In this case, if people who were lost to follow-up were associated with inflammatory markers and periodontitis, the results would be biased. The authors pointed out that healthier participants remained in the study for both time points,² suggesting that selection bias was likely, but we cannot determine its impact on the results. Second, half-mouth assessments may be biased, as partial examination underestimates the prevalence of periodontitis.^{4,5} Third, the present study included change-on-change analysis to evaluate progression of periodontitis over the 2 time points, adjusted for baseline covariates. Based on an analysis of directed acyclic graphs, Rothman et al.⁶ have illustrated that adjusting for baseline covariates in conjunction with change variables can create spurious associations.

To reconcile the study findings in relation to possible bias, we consider the following facts. First, the magnitude of periodontal destruction associated with inflammation was similar to that reported in clinical trials evaluating anti-inflammatory medication and periodontal destruction.⁷ Second, proinflammatory gene variants were positively associated with periodontal disease progression in a recent prospective study.⁸ Third, the effect of inflammation was specific to periodontal destruction and was not related to carious or restored tooth surfaces,² reducing the possibility of confounding by unmeasured factors being an alternative explanation. Finally, the sensitivity analyses were consistent with the main results.²

On balance, therefore, the findings by Pink et al. likely captured the underlying relationship between inflammation and periodontal disease despite limitations of the study. The findings are consistent with the hypothesis that systemic inflammation causes periodontal

destruction. Clinicians need to remember that the inflammatory state may lead to more extensive periodontal disease with more rapid progression.

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