A bidirectional relationship of oral-systemic responses: observations of systemic host responses in patients after full-mouth extractions

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Objective. This investigation tested the hypothesis that systemic inflammatory responses would be attenuated by minimizing the oral microbial burden in patients with moderate to severe periodontitis.

Study Design. Patients (n = 73) scheduled for full-mouth extractions were categorized as case type I/II (gingivitis/mild periodontitis) or case type III/IV (moderate/severe periodontitis). Serum levels of acute phase proteins (APPs) and immunoglobulin G (IgG) antibody were assessed at baseline and through 1 year after extraction.

Results. At baseline, the levels of multiple APPs (e.g., fibrinogen, C-reactive protein) and antibodies to periodontal pathogens were significantly higher with case type III/IV vs I/II. These differences were sustained 12 months after extractions for most APPs.

Conclusions. The results demonstrated that removal of disease by full-mouth extraction of teeth altered the overall burden of challenge to the host. Continued elevation in various APPs in the III/IV group suggested a potential underlying constitutive difference in systemic response characteristics of this population. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:435-444)

Periodontitis is a chronic inflammatory disease elicited by polymicrobial biofilm colonization of the subgingival sulcus around the teeth.[1] This microbial challenge and chronic immunoinflammatory lesion undermines the integrity of the gingival epithelial barrier,[2,3] resulting in destruction of the underlying connective tissue[4,5] and eventual resorption of alveolar bone[6] extending to the point of exfoliation of the teeth.

The disease is most often treated by nonsurgical methods, such as scaling and root planing, combined with oral hygiene. This treatment is generally ineffective in eliminating periodontal pocketing and inflammation in patients with moderate to severe periodontal disease. Because the disease is inflammatory in nature,[7,8] previous cross-sectional studies have suggested a relationship between periodontal disease and various systemic conditions, such as cardiovascular disease, preterm birth, and Alzheimer disease.[9-17] However, randomized controlled intervention studies, aimed at evaluating the effect of nonsurgical periodontal treatment on the systemic condition, have failed to show a beneficial effect.[18-20] In addition, although nonsurgical periodontal therapy alone has some effect in reducing levels of systemic markers of inflammation, such as C-reactive protein (CRP), combination of the mechanical treatment with topical or systemic adjunctive pharmaceutical agents that have anti-inflammatory activities is substantially more efficacious.[4,8,21-25] A clearer understanding of the overall burden of challenge to the individual with regard to chronic inflammatory responses, as well as the genetic[26,27] and environmental[28-30] contributions to this process, could provide more patient-specific information for determination of the contribution of these responses to general disease risks. Considering that the oral-systemic link is most often observed in patients with more severe forms of periodontal disease, a causal effect of periodontal infection, inflammation, and disease on systemic health cannot be demonstrated unless the periodontal condition is eliminated as a potential causative agent.

Our present study uses a model of convenience where patients are being treated for dental disease by electing full-mouth extraction before denture placement. The hypothesis tested in this study was that levels of systemic markers of inflammation and antibody

Statement of Clinical Relevance

Although full-mouth extractions dramatically affected the oral microbial burden and decreased systemic inflammatory biomarkers, systemic inflammation remained elevated in patients with severe periodontitis even 1 year after they became edentulous, suggesting some unique aspects of innate immune response regulation in this group of patients.

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Table I. Demographic data of the participants

Patient group	*n*	*Age (y), median (range)*	*Gender M:F*	*Smoking (%)*	*No. of teeth, median (range)*	*df*	*Periapical infections, % of teeth*
ADA I/II	19	28 (21-49)	18:1	94.8	23 (18-32)	11.2 ± 10.1	26.8 ± 25.8
ADA III/IV	40	45 (24-75)*	29:11	78.5	24 (16-31)	19.2 ± 7.1*	31.3 ± 28.0

All participants were white adults.
ADA, American Dental Association.
*Significantly different at $P < .05$.

responses to the oral infection would decline over time after full-mouth tooth extraction in patients with moderate to severe periodontitis but that similar changes would not be observed in those patients who have elected full-mouth extractions owing primarily to rampant dental caries.

MATERIALS AND METHODS

Study design and participants

The recruitment of human participants for this study was approved by the Institutional Review Board of the University of Kentucky. A longitudinal, intervention study design was used. Inclusion criteria for patients required them to be 18 years of age or older. They were invited to participate in this study if they had at least 15 teeth and had treatment planning through the College of Dentistry for extraction of all remaining teeth before denture placement. No patients were excluded based on race or gender. Specific exclusion criteria included current aspirin therapy, statin therapy, or pregnancy and a history of chronic obstructive pulmonary disease, rheumatoid arthritis, or diabetes. Participants were recruited from patients presenting for treatment in the Division of Oral & Maxillofacial Surgery of the College of Dentistry at the University of Kentucky.

All patients completed a medical history form, which was confirmed by history and physical examination, and patients were confirmed as meeting the inclusion and exclusion criteria. An oral examination and panoramic radiographs were taken at baseline. Patients were classified at baseline, using radiographs, for the presence of periodontal disease using a modification of the American Academy of Periodontology classification system, as follows: case type I, gingival disease with no bone loss; case type II, early periodontitis with slight bone loss (<25%); case type III, moderate periodontitis with moderate bone loss (25% to 50%); and case type IV, advanced periodontitis with major loss of bone (>50%). In addition, the number of teeth radiographically demonstrating periapical pathology was evaluated as a potential indicator of periapical infection. A sample of peripheral venous blood was collected at baseline (day of extractions) and at 1, 3, 6, and 12 months after treatment to examine levels of various systemic host response markers.

Serum acute phase proteins

A Luminex 100 (Luminex Corp) was used for multiplexing analysis, combining enzyme-linked immunosorbent assay (ELISA) and flow cytometry to analyze an array of biomarkers of inflammation of each sample at each time point. These included CRP, haptoglobin, serum amyloid A (SAA), and serum amyloid P component (SAP). Lipopolysaccharide binding protein (LBP), bactericidal/permeability-increasing protein (BPI) and mannose binding protein (MBP)/mannose-binding lectin (MBL) were measured using commercial ELISA tests (Hycult Biotechnology, Cell Sciences, Canton, MA, USA).

Serum IgG antibody levels to *Aggregatibacter actinomycetemcomitans* JP2, *Porphyromonas gingivalis* ATCC33277, *Treponema denticola* ATCC35405, *Tannerella forsythia* ATCC49307, *Prevotella intermedia* ATCC25611, *Fusobacterium nucleatum* ATCC25586, and *Campylobacter rectus* ATCC33238 were determined using an ELISA, as we have previously described.[31]

Statistical methods

An analysis of variance (ANOVA) on ranks for repeated measures was used to estimate changes in levels of the proteins after the surgical treatment (SigmaStat 3.5; Systat Software Inc, Chicago, IL, USA) with post hoc testing using a Holm-Šidák test. Comparison of the levels of the acute phase proteins (APPs) in the type I/II periodontitis vs type III/IV subsets of patients used a nonparametric Mann-Whitney *U* test to examine differences at baseline and at 12 months. Changes in antibody levels from baseline were determined using a Friedman repeated measures ANOVA on ranks. Differences between the patient groups at individual time points were determined using a Mann-Whitney *U* test. A value of $\alpha = .05$ was selected for statistically significant differences.

RESULTS

A total of 73 patients consented to participate in the study. Demographic data of the 59 patients who received extraction of all remaining teeth are provided in Table I. Nineteen of the patients were classified as having periodontal case types I/II, and 40 patients as having case types III/IV, based on radiographic