

# Chronic Oral Inflammation and the Progression of Periodontal Pathology in the Third Molar Region

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**Purpose:** To assess the association between risk markers of chronic oral inflammation and changes over time in periodontal probing depth (PD) in the third molar region, the distal of a second molar, or around a third molar.

**Subjects and Methods:** The data from these analyses are part of a study of subjects enrolled with 4 asymptomatic third molars with adjacent second molars in an institutional review board-approved longitudinal trial. Full-mouth periodontal probing was conducted at enrollment and follow-up. Enrollment levels of periodontal pathogens and gingival crevicular fluid inflammatory mediators were assayed as indicators of the degree of oral inflammation. Subjects were categorized as those who had at least a 2 mm change in periodontal PD between baseline and follow-up in the third molar region and those who did not. The relationship between aggregated subject baseline PD, levels of periodontal pathogens, and gingival crevicular fluid IL-1 $\beta$ , and the proportion of subjects with changes in PD  $\geq 2$  mm versus those with PD  $< 2$  mm were compared with Cochran-Mantel-Haenszel statistics. Level of significance was set at 0.05. Risk assessment models for a change in PD  $\geq 2$  mm were developed using logistic regression analysis.

**Results:** Twenty-four percent of 254 subjects exhibited a change in PD from baseline to follow-up of  $\geq 2$  mm in the third molar region. Of these, 95% had a baseline PD of  $\geq 4$  mm. Both high ( $\geq 10^5$ ) "orange" and "red" complex bacteria and PD of  $\geq 4$  mm detected at enrollment were significantly associated with a change in PD  $\geq 2$  mm. Odds of a change in PD  $\geq 2$  mm were increased if baseline pathogen levels were  $\geq 10^5$  or a PD of  $\geq 4$  mm was detected at enrollment.

**Conclusion:** Our findings are consistent with chronic oral inflammation leading to a progression of periodontal disease in the third molar region.

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Blakey et al<sup>1</sup> reported that for asymptomatic young subjects, at least 1 periodontal probing depth (PD)  $\geq 4$  mm in the third molar region, the distal of second molars, or around third molars, was common. Almost two thirds of those studied had at least 1 PD  $\geq 4$  mm at enrollment. If the third molars had a communication to the oral cavity and could be probed, a PD  $\geq 4$  mm was likely around third molars (61%), but in 41% the distal of second molars was affected. These analyses added weight to Blakey et al's earlier conclusions that periodontal pathology is more common in the third molar region in young adults than clinicians might expect.<sup>2</sup>

For 38% of the subjects with PD  $\geq 4$  mm at enrollment, clinical evidence existed that their periodontal status in the third molar region had worsened in a relatively short time, a median follow-up of 2.2 years.<sup>1</sup> Almost always, 95% of the time, a PD change  $\geq 2$  mm occurred with a baseline PD  $\geq 4$  mm.

White et al<sup>3</sup> documented that subjects with PD  $\geq 5$  mm in the third molar region had elevated levels of "orange" and "red" complex periodontal pathogens detected in biofilm samples from the distal of second molars. For the same patients, they found elevated subject levels of the gingival crevicular fluid (GCF) inflammatory mediator, IL-1 $\beta$ , sampled from the distal of all second molars and the mesial of all first molars, but not PGE<sub>2</sub>.<sup>4</sup> Data documenting periodontal pathology with retained third molars suggested an early stage of periodontal disease in these young adults. For affected subjects, asymptomatic periodontal pathology was a potential source of chronic oral inflammation and an entree or portal to the systemic circulation for pathogenic bacteria.

This study was designed to assess the association in asymptomatic subjects between changes in periodontal status, PD in the third molar region over time, and the periodontal pathogenic bacteria levels detected in oral biofilm samples from the distal of all second molars at baseline. In addition, changes in PD in the third molar region at follow-up were compared with baseline levels of the GCF inflammatory mediator IL-1 $\beta$ .

## Subjects and Methods

The data for these analyses are part of a study of subjects with 4 asymptomatic third molars with adjacent second molars enrolled in an institutional review board-approved longitudinal trial at 2 academic clinical centers, The University of Kentucky and The University of North Carolina. Inclusion criteria for the trial dictated that subjects be healthy (ASA I, II), be between the ages of 14 and 45 years, and have 4 asymptomatic third molars with adjacent second molars. Those with the most severe form of periodontal disease (AAP IV), or who had taken antibiotics within

3 months prior to possible enrollment, were excluded from participation. Subjects were enrolled over a 4-year period ending in 2002.

Demographic data and data assessing oral health were collected from each subject at baseline and at follow-up exams. After data collection, enrolled subjects had a dental prophylaxis at baseline and at each follow-up exam. To be included in these analyses, subjects had to have had at least 2 follow-up exams after baseline. This assured a minimal level of periodontal care for all in the study.

Before collecting baseline biofilm samples for the detection of bacteria and before periodontal probing, GCF samples were taken from the mesial of all first molars and distal of all second molars. GCF samples were independently analyzed by enzyme-linked immunoabsorbant assay for levels of IL-1 $\beta$  as a measure of oral inflammation.<sup>4</sup> Although levels of IL-1 $\beta$  were determined independently at each of the 8 sampling sites, the mesial of all 4 first molars and distal of all 4 second molars for each patient, a pooled patient mediator level was calculated as the mean of the 8 site values and a pooled log mediator level as the mean of the log values from the 8 sites. Log<sub>10</sub> transformations were used to normalize the right tailed skewed distribution of the original mediator values. The anti-logs of the descriptive statistics calculated across subjects, which convert the log values back to the original units, are reported in the tables and text as a patient level indicator of oral inflammation.

At enrollment, subgingival biofilm samples were taken from the distal of second molars in all 4 quadrants of the mouth before periodontal probing. The presence and levels of 11 bacterial species were determined using whole chromosomal DNA probes and checkerboard DNA-DNA hybridization.<sup>5</sup> Based on the findings of Socransky et al,<sup>5</sup> the detected bacterial species were grouped into "red" or "orange" complex bacteria, all associated with periodontitis and chronic oral inflammation. For our study, "red" complex bacteria included *B. forsythus*, *P. gingivals*, and *T. denticola*; "orange" complex bacteria included *P. intermedia* and *C. rectus*. "Red" or "orange" complexes of bacteria were considered present in a subject if the microorganisms could be detected by sampling at the distal of any second molar. The presence or absence of "orange" and "red" complexes of bacteria at levels of  $\geq 10^5$  in the third molar region were tabulated for each subject enrolled in the clinical trial.

Full-mouth periodontal probing, 6 sites each tooth, was conducted as a measure of clinical periodontal status at baseline and follow-up. Because third molar periodontal pathology would directly affect this anatomic region of the mouth, periodontal PD in the third molar region, the distal of second molars (2 PD), or around third molars (6 PD), was the focus of these analyses.

**Table 1. FREQUENCY OF SUBJECTS WHO EXPERIENCED AT LEAST A 2 mm CHANGE IN PD COMPARED WITH THOSE WHO DID NOT BASED ON THEIR PD AT BASELINE**

Patient Baseline PD	PD Change <2 mm		PD Change ≥2 mm	
	n	%	n	%
<4 mm (n = 103)	100	97	3	3
≥4 mm (n = 151)	93	62	58	38
Total (N = 254)	193	76	61	24

NOTE. PD change ≥2 mm is significantly different if baseline PD ≥4 mm,  $P < .001$ .

White et al. *Chronic Inflammation and Third Molars. J Oral Maxillofac Surg* 2006.

The maximum PD of all second and third molars probed were aggregated to the subject level. At baseline, subjects were categorized as those who had at least 1 tooth with a PD ≥4 mm in the third molar region indicating periodontal pathology and those with less than 4 mm PD. For change from baseline, subjects were categorized as those who had at least 1 tooth with an increase of PD ≥2 mm and those who had no teeth exhibiting a ≥2 mm change in PD. A change in PD of at least 2 mm in the third molar region over time was considered primary because this level of change is considered clinically as an indicator of worsening periodontal disease and accompanying increased oral inflammation.

The proportion of subjects with a change in PD ≥2 mm over time, in the third molar region, were compared with those with a PD <2 mm using Cochran-Mantel-Haenszel statistics. The explanatory variables examined were the baseline subject PD and levels of periodontal pathogens. Level of significance was set at 0.05. Risk assessment models for a change in PD ≥2 mm were developed using logistic regression analysis.

## Results

Data from 254 subjects with at least 2 follow-up visits were available for analysis. More were female (56%), and Caucasian (80%). African American patients (13%) were similar in percentages to the US population. Subjects were young adults; mean age at enrollment in the trial was 27.5 years (SD, 7.8 years). Median follow-up from enrollment was 2.2 years (IQ 2.0, 2.6 years). All subjects were asymptomatic at enrollment. None of the subjects reported symptoms at follow-up.

Sixty-one (24%) of the 254 subjects experienced a change in PD of at least 2 mm on at least 1 tooth in the third molar region during the follow-up period (Table 1). The likelihood of a ≥2 mm PD change was increased if the subject had had a baseline PD in a third

**Table 2. FREQUENCY OF SUBJECTS WHO EXPERIENCED AT LEAST A 2 mm CHANGE IN PD COMPARED WITH THOSE WHO DID NOT BASED ON THE "ORANGE" AND "RED" COMPLEX PERIODONTAL PATHOGENIC BACTERIA LEVELS AT BASELINE (n = 204)**

	PD Change <2 mm		PD Change ≥2 mm	
	n	%	n	%
"Orange"				
<10 <sup>5</sup> (n = 122)	102	84	20	16
≥10 <sup>5</sup> (n = 82)	59	72	23	28
	PD Change <2 mm		PD Change ≥2 mm	
"Orange" & "Red"	n	%	n	%
<10 <sup>5</sup> (n = 132)	110	83	22	17
>10 <sup>5</sup> (n = 72)	51	71	21	29

NOTE. Top: PD change ≥2 mm is significantly different if baseline "orange" pathogens ≥10<sup>5</sup>,  $P = .05$ . Bottom: PD change is significantly different if baseline "orange" and "red" pathogens ≥10<sup>5</sup>,  $P = .04$ .

White et al. *Chronic Inflammation and Third Molars. J Oral Maxillofac Surg* 2006.

molar region of a least 4 mm. Ninety-five percent (58 of 61) of those with a 2 mm change over time had had a PD of at least 4 mm at baseline ( $P < .001$ ).

The association between high levels (≥10<sup>5</sup>) of baseline "orange," or "orange" and "red" complex bacteria and the clinical finding of at least a 2 mm change in PD was significant (Table 2). Twenty-eight percent of the subjects had elevated baseline "orange" complex bacteria ≥10<sup>5</sup>, and 29% both complexes ≥10<sup>5</sup> compared with 16% and 17%, respectively, for subjects who did not experience a 2 mm change in PD.

Of subjects who had at least 1 PD ≥4 mm at baseline and a change in PD ≥2 mm at follow-up (53%), 21 of 40 had high levels of baseline pathogens, "orange" and "red" complex bacteria ≥10<sup>5</sup> (Table 3). A stratified analysis confirmed that the relationship between a deep PD at baseline and a change of at least 2 mm was statistically significant ( $P < .001$ ) regardless of whether the "combined" bacteria complex was ≥10<sup>5</sup> or <10<sup>5</sup> (homogeneity of odds:  $P = .20$ ) (Table 3).

However, 33% (24 of 72) of subjects with "orange" and "red" complex bacteria detected ≥10<sup>5</sup> at baseline did not have clinical evidence of periodontal pathology at baseline (PD <4 mm) nor an increase in PD ≥2 mm at follow-up (Table 3). As the time from enrollment in the longitudinal clinical trial lengthens it will be important to determine if clinical evidence of periodontal pathology develops in these subjects.

GCF IL-1β levels tended to be higher if subjects had baseline PD ≥4 mm ( $P = .08$ ), but higher baseline

**Table 3. THE FREQUENCY OF SUBJECTS WHO EXPERIENCED AT LEAST A 2 mm PD CHANGE FROM BASELINE TO FOLLOW-UP (MEDIAN, 2.2 YEARS) VERSUS THOSE WHO DID NOT BASED ON THEIR COMBINED "ORANGE" AND "RED" COMPLEX PERIODONTAL PATHOGENIC BACTERIA LEVELS AT ENROLLMENT AND THEIR MAXIMUM BASELINE PERIODONTAL PROBING DEPTH IN THE THIRD MOLAR REGION (n = 204)**

	Baseline PD	Change in PD at Follow-up	
		<2 mm n (%)	≥2 mm n (%)
"Orange" & "red"	<10 <sup>5</sup>	<4 mm	57 (97)
		≥4 mm	3 (3)
	≥10 <sup>5</sup>	<4 mm	53 (73)
		≥4 mm	19 (27)

NOTE. PD change ≥2 mm is significantly different if baseline PD ≥4 mm and "orange" and "red" pathogens ≥10<sup>5</sup>, P < .001. Relationship between baseline PD and change holds regardless of combined "orange" and "red" levels at baseline, Breslow test of homogeneity of odds, P = .20.

White et al. *Chronic Inflammation and Third Molars. J Oral Maxillofac Surg* 2006.

GCF IL-1β levels were not associated with an increase in PD ≥2 mm at follow-up (Table 4).

"Orange" and "red" complex bacteria ≥10<sup>5</sup> alone doubled the odds of an increase in PD ≥2 mm (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.0, 4.0) (Fig 1). A baseline PD ≥4 mm in the third molar region greatly increased the odds of a change in PD ≥2 mm (OR, 21.0; 95% CI, 6.4, 69.3). If elevated bacteria levels are combined in the same statistical model with a baseline PD ≥4 mm, the baseline periodontal pathogen level is less a factor than baseline PD ≥4 mm (OR, 1.8; 95% CI, 0.9, 3.8 vs OR, 19.7; 95% CI, 4.6, 84.5, respectively).

**Discussion**

Our findings have important clinical implications. "Orange" and "red" complex pathogenic periodontal

bacteria ≥10<sup>5</sup> or a baseline PD ≥4 mm in the third molar region was associated with an asymptomatic, deteriorating periodontal status, an increase in PD ≥2 mm in the third molar region in a short time frame, and a median follow-up of 2.2 years. These data are consistent with a transition from oral health to clinical oral disease with chronic oral inflammation. In addition, periodontal probing in the third molar region appears to be an effective clinical tool allowing clinicians an assessment of periodontal pathology even though patients may have no symptoms.

We report that elevated levels of periodontal pathogens, "orange" and "red" complex bacteria ≥10<sup>5</sup>, found in biofilm samples from our subjects at enrollment, doubled the odds of a worsening clinical periodontal status at follow-up. For almost one third of our asymptomatic subjects, a change in PD ≥2 mm in less than 3 years was associated with elevated baseline levels of periodontal pathogens. This pathway is illustrated in Figure 1.

Socransky and Haffajee<sup>6</sup> reviewed the current biological model of oral biofilm. They emphasized that periodontal disease is a transmissible, infectious disease coupled with colonization of periodontal pathogenic bacteria. "Orange" complex periodontal bacteria almost always become established in periodontal biofilm before "red" complex bacteria. If pathogenic periodontal bacteria are detected at elevated levels, clinical periodontal deterioration is likely. Our data from the third molar region are in concert with this current model of periodontal pathology.

Our analyses from young adults indicated that a baseline PD ≥4 mm in the third molar region was an even more robust indicator of a possible deterioration of periodontal status, a change in PD ≥2 mm. A plausible explanation for the asymptomatic periodontal disease status of our subjects is that decreased oxygen tension is more likely with PD ≥4 mm, facilitating colonization of periodontal pathogens, increased inflammation, and progressive disease. In studies of older patients with periodontal disease over

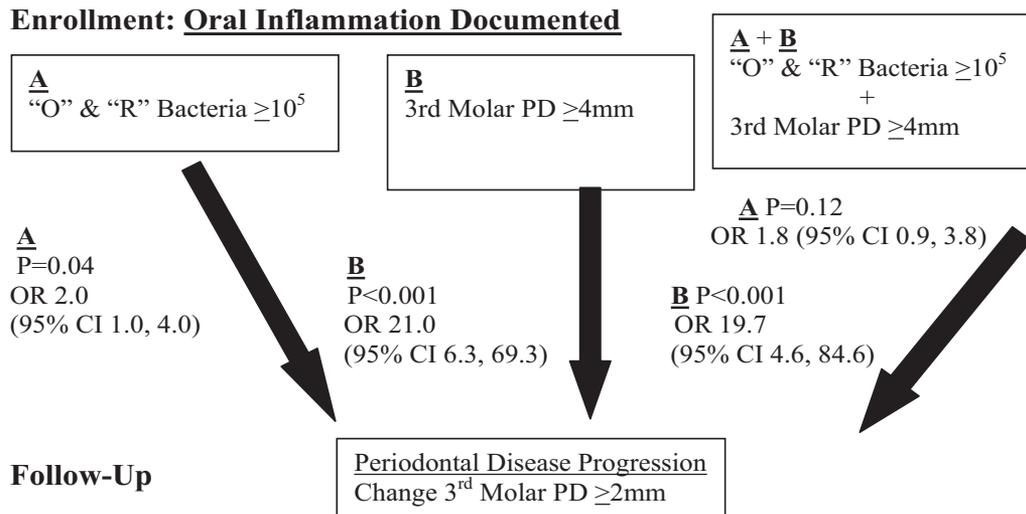
**Table 4. PATIENTS' MEDIAN IL-1β LEVELS AND INTERQUARTILE RANGES (IQ) AT ENROLLMENT COMPARED WITH CHANGES IN PERIODONTAL PROBING DEPTHS (PD) IN THE THIRD MOLAR REGION FROM ENROLLMENT TO FOLLOW-UP (n = 250)**

PD at Enrollment	Change in PD <2 mm	Change in PD ≥2 mm
	n ng/mL (IQ)	n ng/mL (IQ)
All PD <4 mm	100 38.6 (16.6, 35.3)	3 23.3 (21.7, 151.8)
At least 1 PD ≥4 mm	90 53.7 (24.9, 45.6)	57 65.6 (17.8, 43.8)

P value for relationship between baseline IL-1β levels and change in PD: .55.

White et al. *Chronic Inflammation and Third Molars. J Oral Maxillofac Surg* 2006.

### Pathway for Third Molar Periodontal Pathology Progression



**FIGURE 1.** Pathway for third molar periodontal pathology progression. “Orange” and “red” complex periodontal pathogens  $\geq 10^5$  or a periodontal PD  $\geq 4$  mm at enrollment increased the odds of periodontal disease progression in the third molar region.

White et al. *Chronic Inflammation and Third Molars*. *J Oral Maxillofac Surg* 2006.

time, disease progression was more likely when PD was deeper.<sup>7-9</sup> Neither the periodontal status of young adults nor the third molar region has been studied often, adding importance to our findings which complement those from older patients.

Although GCF IL-1 $\beta$  levels were higher for subjects with PD  $\geq 4$  mm in the third molar region, elevated GCF IL-1 $\beta$  levels at enrollment were not statistically associated with progression of periodontal pathology, at least in these younger adults over a short time frame. Champagne et al's<sup>10</sup> review of current concepts of periodontal disease is instructive. Periodontal disease is patient-dependent, not tooth-specific. This implies that the patient's immune response to the colonization of periodontal pathogens in biofilm in both shallow and deeper periodontal pockets affects the degree of chronic inflammation associated with periodontal tissue destruction and the subsequent progression of disease. The immune response in time to the pathogens in the biofilm differs by patient. Levels of GCF inflammatory mediators reflect the intensity of a patient's local and systemic immune response to the composition of the periodontal biofilm. It will be important to see if disease progression, a change in PD  $\geq 2$  mm, also follows with longer follow-up in subjects with higher GCF IL-1 $\beta$  levels at baseline and no change in PD at short-term follow-up.

What are the clinical implications of these findings? Patients and clinicians would be remiss to ignore a PD  $\geq 4$  mm in the third molar region with no symptoms. PD  $\geq 4$  mm reflects a degree of chronic oral inflam-

mation that deserves attention. Over one third of subjects with PD  $\geq 4$  mm at enrollment were found to have an asymptomatic, deteriorating periodontal clinical status affecting the third molar region at follow-up. A deepening PD  $\geq 2$  mm in only 2.2 years is a shorter time frame than clinicians would expect. Erupted third molars were more at risk than impacted third molars. The changes in periodontal status were twice as likely in erupted, vertically positioned third molars as those not at the occlusal plane.<sup>1</sup> Based on our analyses, both chronic oral inflammation with PD  $\geq 4$  mm and high levels of periodontal pathogens were significantly associated with a change in PD  $\geq 2$  mm in the third molar region. This deteriorating periodontal status also provides the pathogens with a ready portal or entree to the systemic circulation in affected individuals.

Can this chronic oral inflammation be treated effectively? As Socransky and Haffajee's<sup>6</sup> review indicated, eliminating periodontal pathogens is a prolonged and difficult clinical task, once bacteria are established in a biofilm that is protective to the bacteria. Periodontal therapy with scaling and root planning, targeted to altering the content of biofilm in periodontal defects, is less effective as PD increases.<sup>9</sup> The more difficult the clinical access, the bony anatomic architecture, and the quality of soft tissue in the third molar region further complicate clinical therapy. In this light, a finding of a PD  $\geq 4$  mm in the third molar region with no symptoms may be sufficient indication for third molar removal.

How do we interpret the elevated levels of periodontal pathogens found in one third of subjects with baseline PD <4 mm and no increase in PD over time (Table 3)? Third molars usually do not erupt until the late teen years. Before this time, third molars may not be exposed to the host oral bacterial flora. Once third molars are exposed, oral biofilm formation follows. Colonization of periodontal pathogens is coupled with periodontal tissue breakdown and periodontal pocket formation (Fig 1). The patient's inflammatory response to the pathogens may accelerate tissue breakdown in susceptible individuals. This pathologic process takes time before the outcome can be detected clinically by periodontal probing. As reported by Blakey et al,<sup>1</sup> the subjects with PD <4 mm tended to be younger (less than 25 years old). If followed for a longer time from enrollment, these subjects with increased levels of periodontal pathogens may develop clinical periodontal deterioration in the third molar region, but they may not. As the time from enrollment lengthens for our subjects, we hope to obtain further data to clarify our findings to date.

In summary, our data suggest that the periodontal status of retained third molars should be clinically monitored at regular intervals by periodontal probing. The absence of symptoms is not a sufficient indication that subclinical periodontal pathology does not exist. Our data from young, asymptomatic subjects with a mean age in the third decade, suggests that increased PD in the third molar region with no symptoms should probably not be ignored. At present no data exist to suggest the optimum treatment for these clinical findings. If a PD  $\geq$ 4 mm in the third molar region is found on clinical exam, clinicians are limited

today to 2 options: either removal of third molars or repetitive, periodic periodontal treatment, attempting to control the levels of periodontal pathogens in the third molar region which will reduce the levels of oral inflammation and the potential systemic exposure.

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