

## Commentary

# Should Our Focus on Inflammation Change the Way We Practice?

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*Some scientists say, “Forget about bacteria; treat, or even better yet, prevent inflammation.” We understand that periodontal diseases originate as bacterial assaults, but some two-thirds of the destruction comes from the inflammatory response to the bacterial invasion. There is growing evidence that inflammation can be transferred from the oral cavity to other parts of the body (and vice versa), explaining the possible association between periodontitis and other chronic inflammatory conditions. As a clinician, I find this intellectually interesting, but when I ask myself whether or not this shift from an infection model to an inflammation model changes the way I treat my patients, the answer is, “not really.” But should it? Have I been so busy in my daily practice that I missed something important? Although I may not understand inflammation on the molecular level, I do know when my patients have inflammation, and when I do what I have been trained to do as a diagnostician and a clinician to eliminate it, most of my patients end up with a good clinical outcome. My job as a clinician is to translate what is going on in research and incorporate it into my practice to provide the best possible patient care. What I offer you in this commentary are the results of my journey to discover how or if our new emphasis on inflammation should affect how I care for my patients. My conclusion at this time is that I should err on the side of aggressive control of periodontal inflammation, since, until proven otherwise, the consequences of undertreatment could be more than the loss of a few teeth. It is your job to decide how this information influences the treatment of your patients. J Periodontol 2008;79:2016-2020.*

### KEY WORDS

Clinical practice; inflammation; periodontal diseases; risk factors.

In an effort to explore how the new emphasis on inflammation may change the way we treat our patients, I studied the literature on inflammation and queried experts in the field to find answers to the questions in Table 1. I confirmed much of what I was already doing in my practice, but I also considered some changes I might make.

### INFLAMMATION AND RISK ASSESSMENT

The real challenge in assessing risk is to identify individuals who are most susceptible to inflammation: those patients with a proinflammatory phenotype, whose response to inflammation seems exaggerated and whose disease seems intractable. How effective are our present tools for identifying these patients before severe attachment loss results? Currently, the answer is, “not very.” Periodontists have been trained in identifying the outward signs of inflammation: changes in tissue color and bleeding on probing that signal vascular proliferation, tissue fragility, and edema. As we monitor attachment levels and probing depths, surrogates for connective tissue remodeling during the inflammatory process and wound healing, we must not forget that clinical presentation does not always correlate with infection and inflammation. Infection with certain bacteria, for example, *Eikenella corrodens*, does not always result in clinical inflammation; the inflammation exists at the biochemical level, but is not clinically visible. Clearly, our patients’ clinical presentations, although important, do not allow us to identify hyperresponders to inflammation in advance. Moreover, as we demonstrated in a series of articles on prognosis,<sup>1-4</sup> clinical parameters, especially in cases of severe disease, were not effective in predicting the fate of teeth.<sup>3</sup> If clinical presentation offers incomplete data, perhaps genetic testing offers more conclusive guidance for assessing risk. Although an innovative chairside test<sup>†</sup> for a gene associated with an exaggerated response to plaque has been developed, both our study<sup>4</sup> and other research<sup>5</sup> found that because of the multifaceted nature of periodontal

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**Table 1.**  
**Questions Regarding Inflammation**

How should inflammation fit into risk assessment?
Is there a way to identify hyperresponders? If so, should these patients be treated differently?
Should new knowledge about inflammation change routine clinical decision making?
Should we change our patient examination? Are there any diagnostic markers for inflammation that are ready for use today?
Should we spend more time on review of systems in our medical history?
Is there a greater role for drugs (local and/or systemic) that modulate the inflammatory response and the treatment of periodontitis? Antimicrobial or anti-inflammatory?
Is there a greater role for drugs (local and/or systemic) that modulate the inflammatory response in regenerative treatment? Antimicrobial or anti-inflammatory?
Should new knowledge about inflammation change the way we maintain our patients? Is there a greater role for drugs (local and/or systemic), and should we maintain questionable teeth?
Are periodontists at risk for not referring patients who have other chronic inflammatory conditions to their physicians?

disease, identification of the interleukin-1 genotype was of limited benefit. Although much of our susceptibility to exaggerated inflammatory response may be genetically influenced, a direct correlation remains unproved. The European Workshop on Etiology and Pathogenesis<sup>6</sup> concluded that “to date there is no clear correlation between any gene polymorphism and clinical indications of inflammation.” Clinical presentation may depend much on lifestyle decisions, such as smoking, diet, and oral hygiene routines.<sup>7-9</sup>

Based on current research,<sup>10</sup> a new set of tools will be available to help identify individuals most susceptible to, and at the earliest stage of, periodontal disease. Currently, a proprietary computerized model<sup>10†</sup> has been developed that helps clinicians determine which patients are at greatest risk for severe periodontitis and helps quantify disease status. Such models cannot directly detect hyperinflammatory patients, but they can detect one of the common characteristics of these patients: failure to respond to traditional therapy focused on antimicrobial control. Computerized systems are sensitive to minor changes in disease status, and they may allow us to identify these hyperinflammatory patients before severe attachment loss occurs. Innovative diagnostics<sup>10</sup> from

genome-association studies and identification of relevant biomarkers found in oral fluids and saliva will give real-time, non-invasive assessment of a patient's status as it relates to inflammation, allowing us to create personalized interventions for each individual. None of these products are ready for clinical practice, however, and other than the growing appreciation for the importance of inflammation on many fronts, when it comes to risk assessment, it is still business as usual.

### THE ROLE OF DRUGS IN CONTROLLING INFLAMMATION

Most mild and moderate periodontal cases are being treated by general practitioners and respond well to traditional periodontal therapy based on principles that have remained unchanged for the past 30 to 40 years. Periodontitis, a bacterially induced inflammatory disease, has always been prevented and treated by limiting microbial insult. The problem now facing most periodontists is to treat effectively those patients who have been referred from general practitioners because conventional therapy has failed. Evidence suggests that severe periodontitis occurs in patients with bacterial insult, systemic inflammation, and altered host response. Systemic inflammation coupled with bacterial insult results in an especially destructive synergy, as evidenced by the presence of severe periodontitis in patients with other inflammatory conditions including cardiovascular disease, pancreatic cancer, osteoporosis, and respiratory disease.<sup>11-15</sup> To treat severe periodontitis, we may need to control both the bacteria and the systemic inflammation, and it makes sense to treat the disease aggressively to arrest periodontal destruction and control systemic consequences. Treatment, as always, begins with microbial control through aggressive mechanical debridement, which initially suppresses the number of bacteria. However, repopulation kinetics show that bacteria come back fairly quickly<sup>16</sup> and can be suppressed considerably if we add a subgingival antimicrobial or systemic antibiotic.<sup>17</sup> The use of some of these adjunctive therapies may be essential in our achieving the systemic effects patients with severe periodontitis require. Tonetti et al.<sup>18</sup> reported that adding antibiotics to scaling and root planing reduces systemic inflammation better than scaling and root planing alone.

The use of drugs in the management of the inflammatory cascade and the host response is more of a challenge but equally important to ensure successful outcomes. Up until 30 years ago, treatment plans were based on the theory that bacteria and their byproducts were the prime culprits in periodontal

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destruction, but at that time, researchers started reporting that the host response to the bacteria had an important impact on disease progression.<sup>5-7</sup> As early as 1985, Williams et al.<sup>19</sup> published an animal study showing that periodontal disease progression was arrested with anti-inflammatory agents. Adverse side effects remained problematic, but proof of principle was there. Research has continued, but both the American Academy of Periodontology<sup>20</sup> and the European Federation of Periodontology<sup>21</sup> state-of-the-science summaries concluded that more long-term clinical trials are necessary to validate adjunctive host-modulation therapy. Currently, the only evidence-based treatment for host modulation is subantimicrobial dose doxycycline. Based on the evidence, one would do well to consider short-term systemic antibiotics or host-modulation drugs along with aggressive mechanical debridement to help control inflammation in patients who do not respond to conventional therapy; have severe disease, especially in the presence of other systemic inflammatory conditions; and smokers or poorly controlled diabetics with mild to moderate disease.

Another implication of the drug/inflammation interaction is the possibility that periodontists may be receiving inadvertent help in treating patients with a hyperinflammatory response because some drugs and technologies developed for systemic disease may also prevent or reduce periodontitis. For example, bisphosphonates prescribed for osteoporosis and other conditions also slow the progression of periodontitis by reducing bone loss.<sup>22</sup> Physicians who treat inflammatory diseases may also inadvertently affect the patient's periodontal condition. After all, inflammation is inflammation. Drugs that treat inflammatory disease may play an important role in the treatment of periodontal diseases<sup>20</sup> because a number of diseases share common mechanisms in their so-called "critical path." In fact, new drug developments in oncology and inflammatory diseases may affect the treatment of periodontal diseases as some companies recognize the periodontal market for prescription drugs as a potential venue for a secondary or tertiary sales arena.

When we treat periodontal diseases, are we also reducing the severity of systemic inflammatory diseases? In some cases, yes. Some studies<sup>18,23</sup> suggest that periodontal therapy improves endothelial function, lowering the patient's risk for cardiovascular disease, and we know that diabetic patients directly benefit when their periodontal disease is controlled.<sup>24</sup> These associations between periodontal diseases and systemic diseases appear to be solid, but many systemic therapeutic benefits of periodontal treatment may take another decade to establish. If more valid connections are found, we can anticipate changes

in the way we practice. For instance, we could see an increase in referrals of periodontal patients with systemic conditions; medical protocols would begin to include periodontal evaluation and management, which would result in more collaboration with medicine in both patient care and research. More collaboration with physicians could mean more competition between periodontists and oral surgeons as to who would be the "go to" source for dental knowledge in the medical world. Also, some physicians may begin treating some periodontal diseases using a new anti-inflammatory or other drugs.

## REGENERATION AND DRUGS

Perhaps the most important factor in successful regeneration is not the membrane or the growth factor, but the degree to which inflammation can be controlled. I cannot forget the 1976 study<sup>25</sup> by Rosling et al. The patients' intrabony defects were treated surgically with the modified Widman flap, but no grafting or regenerative therapy was performed. Every 2 weeks for 2 years, each patient underwent a prophylaxis in addition to being instructed in home care. All patients showed unbelievable radiographic evidence of bone fill achieved without growth factors or membranes, just control of plaque and inflammation. This investigation underscores the role of plaque control in managing periodontal disease and suggests that once inflammation is under control, the environment can be biased into regeneration by the addition of cytokine reservoirs or growth factors. In theory, and in the research laboratory, tissue can be regenerated with various growth factors, signaling molecules, or cell therapies, but in real life, regeneration has been thwarted. For example, there have never been any published studies demonstrating that bone morphogenic protein has never been demonstrated to work effectively around teeth, perhaps because inflammation was not sufficiently controlled. Many new drugs under development to block bone resorption could someday soon be administered following regeneration procedures, adding yet another means to bias the environment toward regeneration. The future may hold many new options, but for now, in regenerative therapy, our traditional methods of reducing plaque and inflammation seem to be the best solutions we have to offer.

## SHOULD NEW KNOWLEDGE ABOUT INFLAMMATION CHANGE THE WAY WE MAINTAIN OUR PATIENTS? SHOULD WE MAINTAIN THOSE QUESTIONABLE TEETH?

These questions, more than any others, compel me to think about changes in my practice. Each of us sees patients in our maintenance programs who suddenly undergo reactivation of their disease after remaining

stable for years during maintenance care, despite compliance in both their home care and recall regimen. The key is that as people age, they change. Whether the change is normal hormonal variation or weight redistribution or gain or the development of hypertension, osteoporosis, or adult-onset diabetes, all are factors that alter the basic systemic inflammatory balance. A suddenly reactivated disease may indicate inflammation at a systemic level, signaling that the person may be developing significant inflammatory conditions outside the oral cavity. Emerging evidence<sup>26</sup> suggests that patients with higher bleeding scores may be hyperresponders to inflammation and more prone to periodontal disease. Minimal bleeding on probing, on the other hand, seems to be a good indicator of low levels of systemic inflammatory biomarkers, which would indicate that the degree of oral inflammation reflects the inflammatory state of the entire body. Therefore, gingival inflammation cannot be viewed as a simple problem, either locally or systemically, especially in high-risk patients. Heavy smokers, diabetics, interleukin-1 genotypes, and those with systemic inflammatory conditions who do not respond to debridement may warrant much more aggressive treatment. Not only should we shorten the recall intervals and reinforce home-care techniques, but also consider recommending toothpastes or essential oils with anti-inflammatory properties or prescribing local delivery drugs, systemic antibiotics, or subantimicrobial dose doxycycline as part of the recall regimen. Because inflammation is associated with systemic events, why take a chance?

All of us have patients in maintenance who have a few teeth that, no matter what I or they do, remain chronically inflamed. Until recently, I felt that as long as the teeth are asymptomatic and not harming adjacent teeth, I would continue to maintain them because this course is the most conservative treatment. Not long ago, I saw a patient who caused me to rethink my strategy. Conscientious about coming in for maintenance every 2 or 3 months, he had almost every inflammatory risk factor. Severely overweight and diabetic, he also worked in a high-stress job and suffered from sleeping problems. Would he be best served, given what we know of the deleterious effect of inflammation on the systemic level, if I retreated those teeth to make maintenance more predictable or extracted those problematic teeth? Evidence<sup>27</sup> suggests that individuals who lost teeth to “refractory periodontitis” can be treated successfully with implants. In a mature practice with a large maintenance population, this change in treatment strategy would be significant. I am not suggesting that the profession should revert to the focal infection theory and endorse wholesale extractions, but I am reconsidering how I should manage this type of

patient in light of our knowledge about systemic inflammation.

### RISK FACTOR MODIFICATION

If we endeavor to reduce systemic inflammation in an effort to improve periodontal outcomes, perhaps I am obligated to inform my patients not only of the traditional risk factors for periodontal disease, but also the risk factors that alter the body's inflammatory balance. For example, the accumulation of fat in the belly, stress, poor sleep patterns, and high fat consumption greatly increase inflammation.<sup>28</sup> Periodontists can inform patients of these risk factors and assist them in finding ways to manage these problems.

Are periodontists liable if they fail to refer patients who have possible systemic chronic inflammatory conditions to physicians? Because we understand that many disorders with inflammatory mechanisms have an impact on periodontal disease, and vice versa, perhaps we should be taking a more detailed systems review during our new-patient examinations and at recall visits to help identify these patients. The Scottsdale Project<sup>29</sup> concluded that dental providers are behaving appropriately when they develop and implement guidelines for identifying patients at risk for diabetes and cardiovascular disease. Perhaps we can prescribe fasting blood-glucose tests for some patients or refer them to their primary care physician. If this sounds inappropriate, remember that, not long ago, many of us were asked why we were monitoring blood pressure. In bringing together experts from medicine and dentistry, the Scottsdale Project reinforced the need for medical-dental collaboration in identifying patients at risk for periodontitis, diabetes, and cardiovascular disease.

### REASSESSMENT

Back to the main question: “Should the movement from an infection model to an inflammation model of the disease change the way we treat our patients?” After review of the evidence and recommendation from experts, the answer for me now is a qualified yes. First, a greater emphasis on inflammation and patient education is indicated. Second, I am considering expanding the medical history to help identify patients who are hyperinflammatory. Third, I plan to err on the aggressive side when I treat hyperresponders by surgically reducing probing depths and making maintenance more predictable, and, when they do not respond to mechanical debridement, I may consider short-term therapy with systemic antibiotics or host modulation to help control inflammation. In those maintenance patients with chronically inflamed teeth, I will consider retreating the teeth with newer technology or extracting them and replacing them with implants. Finally, I will encourage our patients to modify lifestyle risk factors, and I



will begin developing relationships with physicians and creating a wider referral network.

I look forward to reassessing the effect of the inflammation model on our periodontal practices in a few years when we have more evidence to support the already published studies. Until that time, as an advocate for overall health of my patients, I will err on the side of aggressive treatment because I understand that the consequences of undertreatment might be more profound than just the loss of a few teeth.

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