Patients Are Not Equally Susceptible to Periodontitis: Does This Change Dental Practice and the Dental Curriculum?

Kenneth S. Kornman, D.D.S., Ph.D.

Abstract: In the 1960s and 1970s, data became available indicating that most of the adult population had periodontal disease and that effective bacterial removal prevented and treated periodontitis. This information led to a systematic approach to the management of periodontal disease and influenced teaching of periodontics in dental schools. We now know that most adults have only gingivitis and very mild localized periodontitis. A small percentage, albeit representing substantial numbers, of adults have generalized severe periodontitis. We also recognize that a few currently known and measurable risk factors, including diabetes, smoking, and genetics, can identify the patients who are at risk for the severe generalized cases that require extensive therapy and intensive prevention, as well as patients at risk for a less-predictable response to treatment. This review will discuss the evidence that supports the change in our knowledge and understanding of periodontal disease. The question now becomes at what point, and how, do we integrate this new knowledge into the dental curriculum?

Dr. Kornman is Chief Scientific Officer, Interleukin Genetics, Inc. Direct correspondence and requests for reprints to him at Interleukin Genetics, Inc., 135 Beaver Street, Second Floor, Waltham, MA 02452; 781-398-0705 phone; 781-398-0720 fax; kkornman@ilgenetics.com.

Disclosure: Ken Kornman is a full-time employee of Interleukin Genetics, Inc. ILGN develops and markets genetic susceptibility tests and therapeutics for common diseases, including periodontitis, osteoporosis, coronary artery disease, Alzheimer’s disease, and diabetic retinopathy. ILGN has patents issued and pending on cytokine genetic markers, including polymorphisms in the genes for IL-1 and TNFα, and the susceptibility to various diseases and the use of those genetic factors for therapeutic purposes.

Key words: periodontics, periodontology, curriculum, interleukin-1, periodontitis, genetics

Submitted for publication 4/2/01; accepted 6/8/01

The message we have taught dental and dental hygiene students for thirty years is that bacterial plaque causes periodontal disease and regular effective plaque removal prevents and treats the disease. This has been a practical concept that has significantly improved the dental health of much of the population. It is now clear that while bacteria are essential for the initiation and progression of periodontitis, other factors such as smoking and genetics appear to strongly influence the severity of the disease and the response to treatment. New models of how to apply this knowledge to patient care may be necessary in both dental education and dental practice.

Prior to the early 1970s, there were multiple theories as to what caused periodontal disease. Many outstanding dental educators endorsed different theories about the etiology of periodontal disease. It was therefore not uncommon for patients to be treated in substantially different ways, depending on who trained the dentist. In the late 1960s and 1970s studies led, to a great extent, by Harald Löe, Jan Lindhe, and Sigurd Ramfjord demonstrated that inadequate plaque control initiated gingivitis and, over time, led to periodontitis. Most importantly, it was shown that the disease could be predictably treated by focusing on the removal of bacterial accumulations in both subgingival and supragingival areas. Since this information emerged at a time when we were just starting to appreciate the power of hypothesis-directed research, the principles derived from that early research became widely accepted. Research prior to this time had been observational in nature. Observations were made using pathological or clinical material, and then hypothetical explanations were developed to explain what produced those observations. Of course, this approach primarily leads to the development of theories, but does not prove or disprove whether clinical application of any specific theory leads to improved patient outcomes. The big change occurred when physicians and dentists starting actually testing those theories. The experiments by Löe
and colleagues\textsuperscript{1,2} that demonstrated that bacterial accumulations on the teeth were the essential cause of gingivitis were so dramatic and easy to understand that they led to a rapid incorporation of the findings into dental education and practice.

The role of plaque in periodontal disease was reinforced by several epidemiological studies showing a relationship between plaque levels and periodontal disease. There were several implicit conclusions that were disseminated as part of the teaching of the importance of plaque control. It appeared that periodontal disease was ubiquitous in human populations and that the only consistent determinant of disease was plaque control.

Where Does the Individual Patient Fit in This Concept?

However, as oral hygiene habits improved in the Western world and as the ability to measure the severity of periodontitis improved, we began to realize that not everyone appeared equally susceptible to the disease process. In retrospect, although not fully appreciated at the time, a few observations had demonstrated the apparent variability in host susceptibility to a bacterial challenge. Lindhe and colleagues\textsuperscript{3} showed, in an experimental periodontitis study in dogs, that long-term plaque accumulation and gingivitis development led to periodontitis, as predicted. However some of the dogs developed essentially no loss of attachment. Similarly, in tea plantation workers in Sri Lanka,\textsuperscript{4} with no oral hygiene or professional dental care, three distinct patterns of periodontitis were evident, including some individuals who developed only minimal disease (11 percent of the population) and some who developed severe generalized periodontitis (8 percent of the population). As a result, some traditional concepts of the role of plaque in periodontal diseases have changed.

One other major change in our understanding of periodontal disease was the prevalence of different severities. We had taught for many years that over 70 percent of the adult population had periodontal disease. In the 1980s it became evident that most adults had only gingivitis, with approximately 30 percent having one or more sites of periodontitis. In fact, the cases of severe generalized periodontitis comprised only 8-13 percent of adult populations throughout the world.\textsuperscript{5,6}

Based on these data, a refinement of our understanding of periodontal disease has emerged in the past few years and is depicted diagrammatically in Figure 1. It has been known for many years that specific bacteria are essential for the disease process. However, the quantity and types of bacteria have not been sufficient to explain the differences in disease severity. Since the bacterial plaque is essential for the initiation and progression of periodontitis, patients with excellent plaque control will have minimal to no disease, and patients with poor plaque control are likely to develop periodontitis. But most patients are somewhere in between perfect and terrible with their oral hygiene. In fact, most patients who see a dentist regularly do a moderately good job of brushing their teeth, but either do not use interproximal cleaning devices at all or are not consis-

![Figure 1. Bacteria activate the mechanisms in the periodontal tissues that lead to inflammation. The magnitude and quality of those tissue changes are determined not only by the bacteria but also by the patient’s genetics and environmental modifiers, such as smoking. The net result of those factors produces clinical severity of disease.](image-url)
What Determines the Severity of Periodontitis?

In recent years it has become evident that, for many common chronic diseases, there are modifying factors that do not directly cause the disease but rather modify some aspect of the disease to make the clinical condition more severe. Based upon all the findings today, Figure 1 represents an appropriate model of periodontitis, in which the bacteria are still required to initiate the patient’s inflammatory response, but other factors modulate or amplify that inflammatory response to change the clinical presentation of disease.

There are now data to suggest that smoking, diabetes, and genetic influences put certain individuals at a relatively high risk for increased severity of periodontitis. The bacterial challenge initiates inflammation in the tissues; then genetic risk factors and acquired risk factors, such as smoking, amplify the inflammatory response in the tissues and determine the resulting disease progression and severity that is seen clinically as bone and attachment loss.

As a result, we now understand the common form of adult periodontal disease involves basic principles as described in Table 1. Because of this new understanding of the biology and mechanisms involved in periodontal disease, it may now be appropriate to change the teaching and practice of periodontics. Some of the following appear to be key elements of our new understanding:

1. The center of the story is what happens in the tissues. The tissue response is comprised of:
   a) the biochemical interactions that constitute homeostasis and pathologic mechanisms in periodontal connective tissues,
   b) the biochemical interactions that constitute homeostasis and pathologic mechanisms in bone, and
   c) the immuno-inflammatory processes.

2. The story is initiated by ecological changes that lead to an emergence of specific periodontal bacterial pathogens and how therapy prevents these changes. It is, of course, critical to emphasize the arrows in Figure 1. One must consider how biochemical factors produced by the pathogenic bacteria directly interact with the biochemistry of 1a-c above.

3. The risk assessment part of the story is described by:
   a) the specific bacteria that activate the inflammation, and
   b) the genetic and environmental modifiers that alter the body’s response to the bacterial challenge. As discussed below, the modifiers, such as smoking, have become a major part of our new understanding of the clinical management of this disease.

Given the above model, how do genetic variations among patients influence periodontal disease?

Interleukin-1 (IL-1) Is Essential to Periodontal Disease

Many studies throughout the world have shown that three chemicals in the tissues are consistently associated with more severe disease or actively pro-

<table>
<thead>
<tr>
<th>Table 1. Fundamental understandings of chronic periodontitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If the bacteria that accumulate on the teeth are not removed regularly, the ecology and tissue changes favor emergence of specific bacteria in the dental plaque. These specific bacteria “cause” periodontitis.</td>
</tr>
<tr>
<td>• The bacteria that initiate periodontitis do so by activating inflammatory mechanisms in the periodontal tissues that result in a net loss of bone and connective tissues that support the teeth.</td>
</tr>
<tr>
<td>• The degree of activation of inflammation by the bacterial challenge is modified by genetic variations in some individuals and by environmental factors, such as smoking, in some individuals.</td>
</tr>
<tr>
<td>• The body’s response, as evidenced by the amount of clinical disease in a patient, is therefore a result of the specific bacterial challenge and the genetic and environmental modifiers that alter the expression of inflammation in the tissues.</td>
</tr>
</tbody>
</table>
gressing disease. Those chemicals are interleukin-1 (IL-1), prostaglandin-E2 (PGE₂), and the enzymes that destroy collagen and bone, i.e., matrix metalloproteinases (MMPs). These chemicals are important mediators of the inflammatory response and appear to play a central role in bone loss. IL-1 is a primary regulator of both PGE₂ and matrix metalloproteinases. Recent studies showed that specific blocking of IL-1 and TNFα in the gingival tissues, without any plaque control measures, blocked a substantial part of the bone loss in a monkey model of periodontal disease.

There are excellent reviews dealing with the roles of PGE₂ and matrix-metalloproteinases in periodontitis. This review will focus on IL-1 and the genetic factors that regulate IL-1 levels and what that information means to the management of individual patients. There are many reports on IL-1 levels in tissue and gingival crevice fluid (GCF) or IL-1 production from cells and association with bone loss and more advanced or progressive periodontitis. For example, recent studies looking at the severity of bone loss compared to gingival crevicular fluid levels of IL-1 show essentially a straight-line relationship—that is, the higher the levels of IL-1 in the crevicular fluid, the more severe the bone loss.

But there are thousands of chemicals involved in the metabolism of the periodontal tissues, so why should we focus on only a few specific ones? Some of the chemicals sit at the head of multiple biochemical cascades. Therefore, they have the potential to amplify tissue responses—that is, they have leverage on the clinical outcomes. Interleukin-1 appears to be one of the chemicals with great leverage power in certain diseases.

Recently, the critical role of IL-1 in bone destruction was shown in a mouse model (Figure 2). When mice with an intact IL-1 system were ovariectomized to simulate estrogen depletion during menopause, the animals lost substantial bone density. When mice were created with a blockage in the IL-1 system, the estrogen depletion resulted in no bone loss. This suggests that, at least in mice, IL-1 is essential for bone loss after estrogen depletion. IL-1 was found to be an essential part of periodontitis in other studies. The investigators produced periodontitis in monkeys. One group of monkeys was treated with chemicals that specifically block IL-1 and a similar chemical, TNFα. The animals with blocked IL-1 and TNFα developed much less bone loss, in spite of having a heavy bacterial challenge.

Variations in IL-1 Genes Amplify the Body's Response

It has been known for several years that some people produce higher levels of IL-1 than other people. The high producers on one day will also be high producers if examined again at a later date, and high production of IL-1 tends to run in families. It is now known that there are specific IL-1 gene variations that cause high production of IL-1 when that individual is exposed to a bacterial challenge. Ap-
approximately 30 percent of Caucasians have these genetic factors.

In some studies, but not all, peripheral white blood cells incubated in the laboratory with bacterial products from gram-negative bacteria produced significantly more IL-1β if the white blood cells have come from a person who has a specific variation in the IL-1 genes (“genotype positives”). Perhaps most importantly, however, the levels of IL-1 are higher in the periodontal tissues of genotype positives. In recent studies, the IL-1α and IL-1β levels were significantly higher in the gingival crevicular fluid of genotype positive patients than those of genotype negative patients. In fact, in one of the studies, the greatest difference between genotype positives and genotype negatives was found in sites with minimal pocket depth (<4mm). (See Figure 3.)

In addition, bleeding on probing may be considered a clinical indicator of the inflammatory response. Lang and colleagues evaluated over 320 randomly selected patients in a clinical recall program. Out of 139 nonsmokers, genotype positive patients were significantly more likely than genotype negatives to have an increase in the number of bleeding sites during four maintenance visits.

In summary, patients who are positive for the IL-1 genotype tend to have: 1) increased IL-1 levels produced by their white blood cells, 2) increased IL-1 in the gingival crevicular fluid, and 3) increased bleeding on probing.

**Prognostic Tests vs. Diagnostic Tests**

Diagnostic tools are used to identify some aspect of a disease that is already present. Examples of diagnostic tests include not only radiographs but biochemical markers of active bone loss. The evaluation of value for a specific diagnostic is based on the assessment of how well the diagnostic detects the disease change when it is actually present and how well the test avoids being “positive” when there is actually no disease.

Prognostics in medicine and dentistry are intended to forecast risk for future aspects of disease. Since there are no facts about the future, prognostics involve a probability of a future event occurring. All patients are familiar with the concept of forecasts. A weather forecast of a 60 percent chance of rain does not guarantee that it will rain, but given that fore-
cast, most people would select different clothing for the day. Similarly, high cholesterol does not guarantee that one will have a heart attack in the future, but it more than doubles the likelihood of an acute coronary event before a certain age.

Variations in the IL-1 Genes Influence Disease Trajectory

People who are positive for the IL-1 genotype are more likely to have generalized severe periodontitis. In a recent study, ninety subjects with no or minimal smoking history were examined for periodontal disease and IL-1 genotypes. Multivariate regression models demonstrated that a patient’s age, former smoking history, and IL-1 genotype were significantly associated with the severity of periodontal bone loss in adults. For non-smokers or former light smokers (<5 pk-yr), IL-1 genotype positives were more than three times more likely to have moderate to severe periodontal disease than patients who were IL-1 genotype negative.

Variations in the IL-1 Genes Influence Therapy Responses

In a study on a periodontal maintenance patient population, McGuire and Nunn examined patients who had been followed for five to fourteen years after periodontal therapy. They attempted to determine what, if any, factors predicted tooth loss in patients during the periodontal maintenance phase. They found that only two predictors—IL-1 genotype and heavy smoking—were significantly related to future tooth loss. IL-1 genotype positives were 2.7 times more likely to have tooth loss than genotype negatives, and heavy smokers were 2.9 times more likely to have tooth loss than genotype positives. Patients who were both genotype positive and also heavy smokers were 7.7 times more likely to have tooth loss than nonsmokers who were genotype negative. The clinical parameters traditionally used to assign prognosis were found to be valuable only in IL-1 genotype negative patients who were nonsmokers.

In another study, predictors of treatment outcomes were evaluated after guided tissue regeneration (GTR) surgery to regenerate the destroyed periodontal attachment. In forty patients treated with GTR surgery, there was no difference in the clinical outcomes after one year. Four years after the surgery, although the treated sites remained stable (lost <1 mm of clinical attachment) in 73 percent (19/26) of the IL-1 genotype negative patients, sites were stable in only 21.4 percent (3/14) of the genotype positive patients.

It is important to emphasize that chronic diseases, such as periodontitis, involve complex biological interactions over time. The relationship between IL-1 gene expression and a few single-nucleotide polymorphisms describes only one dimension of the biology. On a clinical level, the actual expression of IL-1 in a specific site in a specific patient undoubtedly involves complex interactions among many local and systemic factors.

Other Risk Factors

Periodontists have long observed that their patients who smoked or were diabetic were more difficult to treat. It has become clear in recent years that both smoking and diabetes are significant risk factors for more severe periodontitis and for a less predictable response to therapy.

What Does the Differential Susceptibility to Periodontitis Mean to the Dental Curriculum?

If there are measurable risk factors that change the way periodontal disease progresses and responds to therapy, there are several opportunities for incorporating this information into dental practice and into the dental curriculum.

New information to consider in the dental curriculum includes:
1. The concept and use of prognostic risk factors are well established in certain disciplines in medicine, most clearly that of cardiology. In fact, the Western diet has been dramatically influenced by information on the role of cholesterol in heart disease. Dentists are well trained in the use and interpretation of diagnostic tests, but receive little information on the use and interpretation of prognostic factors. Current technological revolutions in medicine, including genetics and biomarkers, are focused to a great extent on prediction of disease susceptibility or response to therapy.
Since the concept and application of predictive medicine is very different from that of diagnostic medicine, we may use new information on periodontal risk factors to train our students in the use and interpretation of these new tools.

2. Schools have worked hard over recent years to integrate clinical relevance into the basic science courses and to extend the basic science into clinical application. Risk factors involved in periodontal disease, such as diabetes, smoking, and genetics, are best taught by describing how each one influences the biology of disease. This provides an opportunity for integration of clinical and biological sciences at the biochemical and genetic levels.

3. Diabetes and smoking greatly increase demands on the health care system. Training students to manage the risk for periodontal disease can provide an effective and focused mechanism for teaching students about the clinical management of diabetes and smoking.

4. Restorative decisions are primarily made today based on the extent of current tissue destruction, yet one of the critical issues is the prognosis of the periodontal support. Risk factors can be incorporated into restorative programs to train students about assessing the prognosis of proposed restorations and about educating patients to improve the prognosis.

We now know that although most adults have only gingivitis and very mild localized periodontitis, a specific group of adults are at high risk for, and usually develop, generalized severe periodontitis. Diabetes, smoking, and measurable genetic variations in the inflammatory response identify the patients who are at risk for severe generalized disease. These same risk factors have been associated with a less favorable response to treatment. This risk information may be applied to various aspects of dental education, from integrating genetics into clinical practice, to evaluating restorative treatment options.

REFERENCES