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REVIEW ARTICLE

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Clinical and public health implications of periodontal and systemic diseases: An overview

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1 | INTRODUCTION

In the last 50 years, considerable progress has been made in understanding the etiology and pathogenesis of periodontal diseases and their interactions with the host. The evolution of this understanding has occurred in three phases: the etiopathogenic (or host-parasite) era, the risk factor era, and the periodontal-systemic diseases era.

The first era was characterized by landmark investigations into the microbial etiology and pathogenesis of both gingivitis and periodontitis. This research identified specific pathogens, which in combination with early colonizers and moderately virulent organisms, formed complex communities organized as biofilms residing in the subgingival environment. In parallel, other investigations studied the host inflammatory and immune mechanisms in response to this bacterial challenge, and the relevant tissue changes which occur in gingivitis and periodontitis as a consequence of these host–parasite interactions. As these mechanisms became better understood, it was evident that most of the tissue destruction which defined these periodontal diseases could be explained by these host inflammatory and immune responses.

Periodontal diseases were recently reclassified at a world workshop in 2017, making a clear distinction between gingivitis, based on the presence of gingival inflammation evidenced by bleeding on probing, and periodontitis, based on the loss of periodontal tissue support, as manifested through clinical attachment loss and radiographically assessed alveolar bone loss.[1] It has been clearly accepted that gingivitis and periodontitis are independent conditions, and while a patient with gingivitis can revert to a state of health, a patient with periodontitis will remain as such for life, even following successful therapy, what reflects differences in the etiopathogenesis and risk factors associated with the initiation and progression of periodontitis, and also in the risk for a patient with periodontitis to influence other systemic diseases. At this workshop, periodontitis was defined as a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms resulting in chronic nonresolving and destructive inflammatory responses, which progress through periodontal attachment and bone loss.[2,3]

The second era brought understanding of the epidemiological relevance of both gingivitis and periodontitis, and the risk factors which influence or modulate their expression. Some of these risk factors were inherent to the subject, such as its genetic susceptibility, while others were either associated with behaviors, such as a lack of adequate oral hygiene or the habit of tobacco smoking, or were acquired, for instance by experiencing a systemic disease such as diabetes mellitus.

Periodontitis affects about 45%-50% of adults in its mildest forms, rising to over 60% in people aged >65 years. Severe periodontitis is the sixth most common human disease and it is estimated to affect 11.2% of the global adult population.[4] Severe periodontitis is defined by extensive loss of the tooth attachment apparatus, which, if untreated, results in tooth loss, frequently leading to nutritional compromise, altered speech, low self-esteem, and a poorer overall quality of life.[5] Severe periodontitis, therefore, represents a significant healthcare, social, and economic burden, and it is both a source of and a consequence of social inequality throughout the world.

The third era focused on the study of possible associations between periodontal diseases and certain systemic diseases. Since the 1990s, multiple epidemiologic, experimental, and interventional studies have evidenced how periodontitis may also impact systemic health. In fact, periodontitis has been independently associated with the majority of chronic noncommunicable diseases of aging and premature mortality.[6] According to the National Centre for Health Statistics of the Centers for Disease Control and Prevention, the seven leading causes of death in the USA in 2010 were heart disease, cancer, chronic lower respiratory disease, stroke/cerebrovascular diseases, unintentional accidental injuries, Alzheimer's disease, and diabetes.[7] All of these, except for unintentional accidental injuries, are chronic diseases which have been associated with periodontitis.

The evidence supporting the associations between periodontal and systemic diseases was reviewed in 2012 by a panel of experts from the USA and Europe, who focused on the most studied associations (diabetes, pregnancy complications, and cardiovascular diseases).[8-10] These experts concluded that periodontitis contributes to the bacterial burden resulting in a significant systemic inflammatory response, which is likely to act as a contributing factor in the pathophysiology of diabetes, pregnancy complications, and cardiovascular diseases.[8-10]

In the last 5 years, important advances have been made in three areas: (a) understanding the etiopathogenesis of periodontitis; (b) identification of the relevant factors increasing risk of developing periodontal diseases; and (c) increased evidence of the epidemiologic associations between periodontitis and systemic diseases, as well as further knowledge about the mechanisms which explain these associations and their likely public health relevance. Although diabetes, systemic inflammation, pregnancy complications, and cardiovascular diseases are still the main focus of research when studying these associations, more recently other systemic diseases, such as metabolic disease and obesity, rheumatoid arthritis, certain cancers, respiratory diseases, and cognitive disorders including Alzheimer's disease, have been independently associated with periodontitis. In fact, a recent systematic review by Monsarrat et al[11] reported that periodontitis has been linked to 57 systemic diseases and conditions, and that over one third of the clinical trials registered in the field of periodontology were related to the study of the associations between periodontal and systemic diseases.

This review describes the emerging evidence and updates the current state of knowledge regarding the associations between periodontal diseases, mainly periodontitis, and several systemic diseases. It starts with an updated review of the roles of the microbiota, inflammation, and genetics in the etiopathogenesis of periodontitis, with the purpose of providing a better basis for understanding the mechanisms, which explain the association between periodontal and systemic health.

2 | SUBGINGIVAL MICROBIAL COMMUNITIES

Curtis et al[12] describe the current knowledge regarding subgingival microbial communities, which are composed of bacteria, archaea, fungi, and viruses, and are associated with the etiopathogenesis of periodontitis. The use of modern molecular techniques, mainly 16S rRNA gene sequencing, has enabled understanding of the complexity and diversity of this microbiota, with more than 500 species estimated to exist within the subgingival plaque. As a consequence of a lack of oral hygiene, different degrees of dysbiosis occur as bacterial masses accumulate, and these shifts towards increasing numbers of gram-negative morphotypes, including rods, filaments, and spirochetes, correlate with the appearance of clinical inflammation of the gingiva and the development of gingivitis. The development of periodontitis is not so clearly understood, being associated with profound shifts in the composition of subgingival communities, and the emergence of overt pathogenic bacteria such as *Treponema denticola*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and other as of yet uncultivated species, which have been clearly associated with deep periodontal pockets. The mechanism through which these pathogens become dysbiotic is probably via disabling and deregulating the efficacy of the host immune and inflammatory systems, and this failure to resolve local inflammation induced by bacteria in the periodontium results in a chronic inflammatory state leading to periodontal tissue destruction.

3 | THE ROLE OF INFLAMMATION AND GENETICS IN THE PATHOGENESIS OF PERIODONTAL DISEASES

In the work by Loos and Van Dyke,[13] the role of inflammation and genetics in the pathogenesis of periodontal diseases is reviewed. Recent epidemiologic data on the age of occurrence and geographical distribution of periodontitis indicate that genetic susceptibility factors are more pronounced in certain racial/ethnic populations, although at subject level its immune function is regulated by a variety of determinants, both intrinsic and acquired. Because the central component of the pathobiology in periodontitis indicates that an aberrant immune response to the dysbiotic bacterial challenge is the main mechanism in periodontal tissue and alveolar bone breakdown, an understanding of both the intrinsic and extrinsic factors influencing this response is key to our understanding of how gingivitis progresses to periodontitis.

On the basis of epidemiologic studies in twins and in families with a high rate of early-onset periodontitis, in younger patients the genetic contribution may be significant. Among these inherited risk factors, at least 65 genes have been suggested as associated with periodontitis based on genome-wide association studies and candidate gene case control studies. This polygenic contribution modulates the differential expression of the immunologic responses, which may concur with other chronic inflammatory diseases such as coronary artery disease, diabetes, metabolic syndrome, obesity, and the so-called systemic inflammatory phenotype.

In addition to these individual variations in genomic sequences, there are epigenetic modifications of DNA that are in part acquired during life, but which can also be inherited. It has been established that aging, microbial exposure, dietary factors, systemic conditions (eg, obesity, diabetes, osteoporosis, and depression), and environmental factors (eg, pollution), as well as modifiable risk and lifestyle factors such as smoking, poor diet and nutrition, psychological stress, and alcohol consumption, have the capacity to induce these epigenetic changes, and may also have a significant impact on the subject's immune function.

The current state of knowledge supports a key pathogenic role for nonresolving chronic inflammation triggered by the dysbiotic changes occurring in the subgingival biofilm. The systemic translocation of these local immune responses, as well as some of the

pathobionts, to distinct distant organs, together with the presence of common genetic factors favoring a hyper-inflammatory response, may help explain the complex associations between periodontitis and other comorbidities such as cardiovascular disease, diabetes, and rheumatoid arthritis.

4 | PERIODONTITIS AND DIABETES MELLITUS

The association between periodontitis and diabetes mellitus is covered in three reviews,[14-16] the first of which considers epidemiologic studies assessing diabetes as a risk factor for periodontitis.[14] Cross-sectional studies clearly demonstrate that subjects with diabetes experience more periodontitis compared with subjects with normal glucose levels at all age levels. Longitudinal studies also demonstrated that the incidence or number of new cases of periodontitis was 2-3-fold higher in individuals with type 2 diabetes compared with those individuals with normal glucose levels. Similarly, the progression of periodontitis and the rate of tooth loss was significantly higher among patients with diabetes and poor glycemic control (mean HbA1c > 7.5%) compared with those with diabetes and good glycemic control (mean HbA1c < 7%), and also with nondiabetics. Common nonmodifiable risk factors common to diabetes and periodontitis include higher age, male gender, minority race/ethnicity, low socioeconomic status, and genetic predisposition, while modifiable risk factors common to diabetes and periodontitis include smoking, excessive alcohol consumption, obesity, physical inactivity, and excessive refined sugar consumption.

Polak et al[15] discuss the mechanisms explaining this comorbidity (diabetes and periodontitis), either through the existence of common risk factors or as a result of causal associations. Among the possible mechanisms, diabetes appears to directly influence the oral microbiome, inducing the dysbiotic state of the subgingival biofilm. This has been demonstrated by studies showing significant differences in microbial profiles when diabetic and nondiabetic subjects were compared, although overall the scientific evidence of microbiota changes in poorly controlled diabetes is not particularly clear. The best studied explanation for the comorbidity between diabetes with poor glycemic control and periodontitis is the inflammation pathway. Inflammation as the linking mechanism has been demonstrated when studying cytokine levels, with clear evidence that subjects with poor glycemic control and untreated periodontal disease display elevated serum, saliva, and crevicular fluid levels of pro-inflammatory cytokines, as well as elevated inflammatory markers within the periodontal tissues.

Experimental animal studies have corroborated these results, supporting that diabetes and hyperglycemic conditions directly induce a hyper-inflammatory state in the infected periodontal tissues. Similarly, in vitro data evidences the links between hyperglycemia and the function of periodontal ligament cells. The hyperglycemic state induces the production of high levels of advanced glycation end products in the periodontal tissues, inducing a hyper-inflammatory state which affects the cellular response. Further studies have also corroborated the pathogenic role of hyperglycemic states, with the release of adipokines which further enhance inflammation, and enhanced osteoclastic activity leading to further bone destruction.

Genco et al[16] review the effects of periodontal disease on glycemic control, and on the incidence of diabetes mellitus and diabetic complications. In this study, several systematic reviews investigating the effects of periodontal disease on glycemic control in diabetic individuals clearly showed a worsening of glycemic control over time in subjects with periodontitis. There is also strong evidence that diabetic subjects with periodontitis experience more severe diabetic complications than those with little or no periodontitis. Moreover, subjects with diabetes and periodontitis show a higher mortality rate, both for cardiovascular death and for all-cause mortality. This study[16] also reviews the evidence of the effects of periodontal treatment on glycemic control in subjects with diabetes. Nine systematic reviews published during 2013-2017 evaluating the reduction in HbA1c at 3-4 months after periodontal treatment showed a reduction in HbA1c, ranging from −0.27% to −1.03%. There was also a reduction in fasting plasma glucose, ranging from −8.95 to −9.04 mg/dL, which was consistent with the reduction in HbA1c. Such a reduction in hyperglycemia, if prolonged, could reduce diabetic complications and improve quality of life.

Genco et al[16] also review the pathologic mechanisms by which periodontitis adversely affects glycemic control, and complications in subjects with diabetes, mainly through the inflammatory response, characterized by secretion of host-derived mediators triggered by the host–parasite interactions. The dumping of these mediators to the bloodstream triggers systemic inflammation, which contributes to insulin resistance and eventually leads to hyperglycemic states and diabetic complications. Moreover, diabetes is frequently linked to obesity, and both of these comorbidities are associated with an intrinsic systemic hyper-inflammatory state.

5 | PERIODONTITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Three reviews[17] deal with the association between periodontitis and atherosclerotic cardiovascular disease. The first review[17] deals with the association of periodontitis with atherosclerotic disease based on epidemiologic studies, the second[18]discusses the possible mechanisms which make these associations biologically plausible, and the third[19] gathers evidence regarding the effects of periodontal therapy on cardiovascular risk.

In the first of these reviews,[17] available evidence regarding the association between cardiovascular disease and periodontal diseases is discussed, covering both clinical studies and the biological plausibility of these links. The evidence from clinical epidemiologic studies support the fact that the incidence of atherosclerotic disease is higher in individuals with periodontitis compared with individuals without periodontitis, irrespective

of the presence of several common risk factors. The magnitude of these associations, however, shows substantial variability depending on the exposure (severity of periodontitis), and in general it is modest (odds ratios between 1 and 2). With regard to biological plausibility, two aspects were reviewed: (a) the microbiologic mechanisms, based on studies demonstrating that periodontal pathogens can reach the vascular tissues, invade the affected cells, and can be found in atheroma plaques. Furthermore, there is evidence from different animal models that periodontal bacteria can induce or promote atherosclerosis; and (b) the possible inflammatory pathways linking both diseases, either by the dumping to serum of the locally generated high levels of pro-inflammatory mediators, matrix metalloproteinases, or elevated nitric oxide, or through changes in the lipid profiles, or thrombotic and hemostatic markers, which may influence systemic inflammation.

In an updated review of these mechanisms, Schenkein et al explain the association between periodontitis and atherosclerotic disease. These generally fall into two categories: (a) microbial mechanisms, which through vascular invasion may locally affect the development of the atheroma lesions; and (b) inflammatory and immunologic mechanisms that directly influence the pathobiology of the atheroma lesion.[18] Different studies have clearly demonstrated that bacteria from the subgingival biofilm can reach the blood circulation and propagate to distant organs and tissues. There is, however, no unanimity on the frequency or the biologic impact of these bacteremia events. Nevertheless, there is indirect evidence of bacterial invasion of endothelial cells and passage to the blood circulation from the identification of periodontal bacterial DNA in atheromatous plaques. In addition to the direct entry of bacteria to the bloodstream, a conceivable indirect route, which has been demonstrated in animal studies, involves the direct invasion of oral bacteria by host immune cells, mainly phagocytic and dendritic cells. Also, animal studies have shown that by inoculating selected periodontitis-associated pathobionts, atherogenesis was induced through several mechanisms.

The mechanisms related to the inflammatory immune response have been clearly elucidated, by either the dumping to serum of inflammatory mediators originating from the periodontium, or via systemically induced inflammatory mechanisms coupled with platelet or dyslipidemia activation. Moreover, there are a number of antibodies or bacterial antigens hyper-expressed in patients with periodontitis that may act through "molecular mimicry" mechanisms by promoting or influencing systemic or local inflammatory responses.

The review by Orlandi et al[19] updates the most recent evidence regarding the impact of periodontal therapy on cardiovascular outcomes. Although randomized controlled trials have shown that periodontal therapy can reduce serum inflammatory mediators, improve the lipids profile, and induce positive changes in other surrogate measures of atherothrombosis, there is no evidence to indicate that adequate periodontal therapy is able to reduce the risk of cardiovascular disease or the incidence of cardiovascular disease events, such as myocardial infarction and stroke in patients with periodontitis.

6 | METABOLIC SYNDROME AND ITS ASSOCIATION WITH PERIODONTITIS

Jepsen et al[20] examine metabolic syndrome and its association with periodontitis, with an emphasis on obesity. Metabolic syndrome is a group of conditions defined by the presence of obesity, dyslipidemia, hypertension, and hyperglycemia, leading to an increased risk of diabetes and cardiovascular disease. Obesity was defined as a complex multifactorial chronic disease leading to abnormal or excessive fat accumulation, which presents a health risk. The association between obesity and periodontitis has been reported in more than 10 recent systematic reviews and these associations have been explained by a synergistic comorbidity effect on systemic inflammation resulting in metabolic dysregulation. In obesity there is an intrinsic association between excess nutrition and innate immune system activation, resulting in obesity-induced inflammation which involves numerous organs including the pancreas, liver, skeletal muscle, heart, and brain, in addition to adipose cells. In periodontitis there is also the presence of systemic inflammation triggered by both microbial and inflammatory mechanisms. Moreover, in this study,[20] there is a review of the potential independent pathogenic mechanisms between periodontitis and dyslipidemia, and hyperglycemia and hypertension, which are also linked to both obesity and metabolic syndrome. In regard to metabolic syndrome, recent systematic reviews have demonstrated a positive association with periodontitis, although the magnitude of the association is modest (OR 1.38 [95% CI, 1.26-1.51]), and most of the available data are derived from cross-sectional studies.

7 | PERIODONTITIS AND ADVERSE PREGNANCY OUTCOMES

Two reviews[21] deal with the associations between periodontitis and adverse pregnancy outcomes, the first of which[21] reviews epidemiologic studies assessing these associations. However, despite the existence of several studies reporting a significant association between periodontitis and adverse pregnancy outcomes, there is no clear evidence of an independent association because contradictory findings are reported in the literature.[21] There are many studies from different parts of the world demonstrating a significant association between periodontitis and low birth weight, preterm birth, and pre-eclampsia after adjusting for potential confounders, but there are other studies which do not show a significant association. These contradictory findings have been explained by the use of different definitions of periodontitis and a wide variety in the reported prevalence of periodontitis in pregnant women across different studies. Similarly, an evaluation of intervention trials assessing the impact of periodontal therapy on

the incidence of adverse pregnancy outcomes produced heterogeneous results. In fact, a recent comprehensive Cochrane systematic review showed that there were no differences in the incidence of preterm birth (RR, 0.87; 95% CI, 0.70-1.10) between pregnant women who were periodontally treated during pregnancy and those who went without treatment.

Figuero et al[22] review the different types of adverse pregnancy outcomes and the experimental evidence behind the mechanisms linking periodontitis with an increase in their incidence. Both direct and indirect mechanisms are discussed. In the direct mechanisms, oral microorganisms (or their components) have the capability to invade the feto-placental unit via hematogenous dissemination, or via an ascending route from the genitourinary tract. These local infections trigger a direct inflammatory reaction leading to different adverse outcomes. The indirect mechanisms are mediated by inflammatory mediators locally produced in periodontal tissues, which once dumped into the circulation may directly affect the feta-placental unit, or, by reaching the liver, may trigger a systemic inflammation state through the release of acute phase protein, such as C-reactive protein, which would then impact the feto-placental unit.

8 | PERIODONTAL DISEASE AND ITS ASSOCIATION WITH CHRONIC DISEASES

Four reviews[23-26] deal with periodontal disease and its association with different chronic diseases, namely, rheumatoid arthritis,[23] cancer,[24] respiratory disease,[25] and Alzheimer's disease and other cognitive disorders.[26]

8.1 | Periodontitis and rheumatoid arthritis

Bartold and Lopez-Olivia[23] update the evidence that has emerged in the last 5 years regarding the relationship between periodontitis and rheumatoid arthritis. This evidence includes both human and animal studies. The animal studies focused on studying the occurrence of citrullination and peptidyl arginine deiminase activity within the periodontium in patients with periodontitis and its potential relation to subsequent development of arthritis. This research has mainly focused on the role of *P. gingivalis* as the main source of this hyper-citrullination activity. The evidence from human studies is derived from many studies with a wide geographical spread and large populations, which have reported an epidemiologic association between periodontitis, tooth loss, and rheumatoid arthritis.

8.2 | Periodontal disease and cancer risk

Nwizu et al[24] provide a comprehensive evaluation of existing epidemiologic evidence concerning the association of periodontal disease and cancer risk, with an emphasis on research published in the last 5 years. Plausible mechanisms linking periodontitis and cancer risk are discussed, as well as important knowledge gaps and future directions for research. Although there are few published epidemiologic studies on periodontal disease and the incidence of total cancer, these largely point to a positive association. Most studies have focused on the link between periodontitis and the risk of head and neck cancer, the majority of which report a positive association. A number of studies have also examined the association between periodontal disease and cancers of the digestive tract. There are strong indications that periodontal disease is positively linked to oesophageal cancers. However, when studying the evidence regarding gastric cancer, the relationship is unclear. The association between periodontal disease and pancreatic cancer risk has yet to be fully determined. However, several studies have shown a possible oncogene linked to pancreatic cancer derived from colonization of periodontal pathobionts, mainly *P. gingivalis*. Similarly, in the association between periodontitis and colorectal cancer, although the existing epidemiologic data do not currently support a positive association, there are many experimental studies linking the colonization of periodontal pathobionts, mainly *Fusobacterium nucleatum*, with a possible oncogene linked to colon cancer. Other cancers, such as lung cancer or breast cancer, have shown a possible synergistic effect between periodontal disease and smoking in regard to the cancer risk.

8.3 | Oral and pulmonary microbiomes

In Mammen et al,[25] the interactions between the oral and pulmonary microbiomes are discussed, mainly the host–pathogen interactions related to the oropharyngeal microbiome or its metabolites, which may propagate to other respiratory organs including the lung. The proximity and continuity of the oral cavity and the lower respiratory tract provides evidence of a shared flora between the oral cavity and the lung and how this continuity in the microbiome may influence the association between periodontal diseases and different pulmonary pathology, mainly when the host defense mechanisms are defecting to prevent this infective spread. A particular focus was placed on pneumonia, chronic obstructive pulmonary disease, cystic fibrosis, and asthma.

8.4 | Periodontitis and its association with Alzheimer's disease and other cognitive disorders

Kamer et al[26] describe the possible role of periodontal disease in Alzheimer's disease and other cognitive disorders by evaluating the current evidence from epidemiologic studies and the experimental evidence describing the plausibility of those associations. In general, most of the studies support an association between periodontitis and different degrees of cognitive alterations, although long-term exposure may be necessary for the association to occur. In regard

to mechanisms, both the inflammatory and the pathogen hypothesis are discussed. In the inflammatory hypothesis, long-term exposure to systemic inflammation and shared genetic factors may account for a significant association between periodontitis and a chronic state of neuroinflammation. The pathogen hypothesis is based on the evidence that oral pathogens, viruses, or their antigens cross the hemato-encephalic barrier and cause direct inflammatory changes in the brain.

9 | PERIODONTAL HERPESVIRUSES

In another study, Slots[27] reviews how herpesviruses and bacteria may interact synergistically to produce periodontal breakdown, and how periodontal herpesviruses may also contribute to systemic diseases.

10 | PATIENT-BASED OUTCOMES INCLUDING QUALITY OF LIFE

This review finishes with a study[28] that covers a relatively new topic in periodontal medicine, that of patient-based outcomes including quality of life. The concept of Oral Health Related Quality of Life is described, as well as different methods for its assessment and application. Also, studies assessing the impact of gingivitis and periodontitis on Oral Health Related Quality of Life are described and discussed.

11 | CONCLUSIONS

The field of periodontal medicine is highly dynamic with new topics and disease associations appearing in rapid succession as a consequence of the exponential increase in scholarly publications. As in other areas of biomedical research, the clinical application of this knowledge usually lags behind the knowledge base, mainly because of the lack of clear and convincing clinical trials demonstrating a significant effect of prevention or of treatment of periodontitis on most of these conditions epidemiologically associated with periodontitis. This may be different in diabetes, where the evidence from interventional studies is beginning to accumulate.

Unfortunately, Professor Robert Genco, the coeditor of this work, did not witness the completion of this review, into which he had put so much work and dedication. Professor Genco has probably been the most prolific author and scientist in this area of periodontal knowledge, focusing on the associations between periodontal diseases and certain systemic diseases, so-called periodontal medicine. His scientific contributions on the links between periodontitis, diabetes, and cardiovascular diseases are seminal in our current knowledge, and this evidence has led the way to many conferences, symposia, and workshops between experts in diabetes, cardiovascular disease, and periodontology analyzing the public health implications and preventive measures needed to address these interactions.

We highly appreciate the efforts made by the authors, which, together with their scholarship and clear writing, have made this review a very valuable document in modern periodontology and dentistry. I am sure that all of the authors cited in this review would dedicate their work and contributions to Professor Robert Genco, to whom we all owe huge recognition for this superb work, and we hope that this, his final contribution, will be further proof of his immense scholar stature.

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