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Age and Periodontal Health – Immunological View

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Abstract

Purpose of the Review: Aging clearly impacts a wide array of systems, in particular the breadth of the immune system leading to immunosenescence, altered immunoactivation, and coincident inflammaging processes. The net result of these changes leads to increased susceptibility to infections, increased neoplastic occurrences, and elevated frequency of autoimmune diseases with aging. However, as the bacteria in the oral microbiome that contribute to the chronic infection of periodontitis is acquired earlier in life, the characteristics of the innate and adaptive immune systems to regulate these members of the autochthonous microbiota across the lifespan remains ill defined.

Recent Findings: Clear data demonstrate that both cells and molecules of the innate and adaptive immune response are adversely impacted by aging, including in the oral cavity, yielding a reasonable tenet that the increased periodontitis noted in aging populations is reflective of the age-associated immune dysregulation. Additionally, this facet of host-microbe interactions and disease needs to accommodate the population variation in disease onset and progression, which may also reflect an accumulation of environmental stressors and/or decreased protective nutrients that could

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Conflict of Interest

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function at the gene level (ie. epigenetic) or translational level for production and secretion of immune system molecules.

Summary: Finally, the majority of studies of aging and periodontitis have emphasized the increased prevalence/severity of disease with aging, all based upon chronological age. However, evolving areas of study focusing on “biological aging” to help account for population variation in disease expression, may suggest that chronic periodontitis represents a co-morbidity that contributes to “gerovulnerability” within the population.

Keywords

aging; periodontitis; immunology; environment; nutrition

Introduction

Aging is a degenerative process with hallmarks of chronic inflammation and oxidative stress-related damage that contribute to deleterious processes that can affect normal cellular functions [1]. Aging populations have demonstrated routine alterations in both innate and adaptive immunity, the combination of which has been termed “immune aging” or “immunosenescence” to describe a deteriorating immune response capacity [1]. It appears that the absence of a well-regulated immune response contributes to aging individuals presenting with a chronic systemic inflammatory state, termed “inflammaging” [2]. Clear evidence supports that this heightened untoward inflammation, contributing to a degenerative process with oxidative stress-related mitochondrial damage and deleterious processes within cells affecting normal cellular functions, is influenced by genetic and environmental factors [3] [4]. The amalgamation of these altered responses distorts immunocompetence enabling the expression of a myriad of diseases associated with aging including autoimmunity, cancer, susceptibility to various infections, and decreased efficacy of vaccine responsiveness [2, 4, 5]. It has been suggested that a lifetime of stress to the body influences the rate and level of immunosenescence, such that an accumulation of radiation, and chemicals and disease exposures likely accelerates the rapidity of the deterioration of the immune system and variation in the individual expression of these immune alterations (Figure 1).

This deterioration of the immune system has generally been described for aging populations, although a substantial increase in variation of response patterns is clearly associated with aging at the individual level. Thus, the variation in immune system capacity and functions remains somewhat ill-defined for specific individuals that will require more detailed studies to determine critical regulators for these altered immune states and how they most accurately reflect chronological and biologic age [6].

Aging and Periodontitis

While epidemiological data is clear that periodontitis increases significantly in prevalence and severity with aging, the fundamental biological mechanisms generating this susceptibility remain ill-defined [7–9]. Furthermore, the disease demonstrates a

disproportionate increase in aged minority individuals and males, various systemic diseases, and related to socioeconomic status, and even geographic location [10].

Investigations of immune responses in periodontitis have included immune response genes and genetic polymorphisms in susceptibility, shifts in host-microbial equilibrium, a range of assessment of inflammatory responses, a broad repertoire of innate immune reactions, and both T cell-based cellular immune responses and the B cell-based humoral immune responses [11–18]. This array of responses has been shown to develop both systemically and within the local oral environment, *e.g.* gingival tissue, crevicular fluid, saliva [19, 20]. Reductionist studies using rodent models and targeting individual biomolecular pathways [21–23][24–28] generally cannot address the systems biology of the host-microbe interactions necessary to delineate the multivariate changes that occur in health and with disease during aging in humans [1]. Findings across the populations suggest that a threshold proinflammatory status exists leading to the adverse effects of immunosenescence and inflammaging of “unsuccessful aging” [29–31]. In this regard, Franceschi et al. [29] have proposed the need for a “network theory of aging” emphasizing the broad-based impact on host response systems to respond to and effectively manage the range of deleterious challenges, in spite of the progressing intrinsic inflammaging environment. These concepts emphasize continuing needs for cutting-edge documentation of human or human-like models of aging, immunosenescence and disease [32].

Aging individual’s exhibit increased susceptibilities to a number of autoimmune, infectious, and inflammatory diseases, including periodontitis [33–36], with physiological loss of periodontal attachment and alveolar bone [34, 36, 37]. Only in the presence of persistent periodontal inflammation do pathological changes in clinical parameters of soft and hard tissue lead to loss of function occur [36–39], which are reported in a significant proportion of the aged population [34, 40]. Beyond the identification of elevated inflammatory mediators in periodontal lesions, substantial evidence has been obtained regarding the role of innate immune responses in chronic periodontitis [41]. This has also been coupled with extensive description of local and systemic adaptive immune responses to oral bacteria considered to be pathognomonic for the disease [13, 19, 42, 43]. More recently definition of the gingival tissue transcriptome has “cast a broad net” that identified a multiplicity of host response differences in disease [44–50], including all aspects of the host response to the bacterial insult to the periodontium. This review will provide some insights into the interrelationships within the host response armamentarium, and relate the interactions to aging effects on both modifiable and non-modifiable factors to enhance disease risk (Figure 2).

As noted in a recent review by Lamster [51], there exists dramatic data regarding aging of the global population. In this report he emphasizes the breadth of noncommunicable diseases (NCD) across this aging population with an array of intrinsic and extrinsic (*e.g.* pharmacopeia of drugs) factors that can adversely impact oral health. Finally, he emphasizes the importance of the field of periodontics evolving over the next decades to better integrate emerging knowledge on aging processes with improved patient oral health wellness and clinical decisions for most effective disease management within the context of systems alterations in aging [52].

Aging and Inflammatory Responses and “Inflammaging”

Aging individuals exhibit an increased susceptibility to a number of inflammatory and degenerative pathologies that include periodontitis, although the underlying causes remain poorly understood. While data suggest that most innate immune cell populations either remain stable in size or slightly decrease with age [53], many aspects of innate immune cell effector functions are decreased in aging, including the normal function of neutrophils, macrophages, dendritic cells, and NK cells that are primary innate immune cells that infiltrate the inflammatory milieu of periodontal tissues during disease. Neutrophil chemotaxis is significantly impaired [54, 55], including both the migration and egress from inflammatory sites [53] that would be expected to affect the initiation and resolution of inflammation in aging [56]. Neutrophils from older individuals also demonstrate impaired phagocytosis, a diminished capacity to kill phagocytosed microorganisms [57, 58], and decreased NETosis [57, 59]. Thus, these functionally compromised neutrophils [60] coupled with age-specific changes in the antimicrobial arsenal of neutrophils and more limited capacity for cross-talk with other immune cells for inflammation resolution [61] would effectively lower resistance to infection in aging populations. Through these altered neutrophil functions and heterogeneity, there would be an increase in the release of hyperinflammatory and toxic substances (eg. degradative enzymes), which could initiate and perpetuate damage to the periodontal tissues [36, 62] (Supplemental Figure 1).

Aging and Innate Immune Responses

Activation of the aged innate immune system results in a dysregulated basal inflammatory response to stimulation, and a diminished efficiency of innate immunity functions [63] (Figure 2). Data support that the numbers and proportions of innate immune cells within the overall host response repertoire, as well as alterations in the cellular functions appear to be critical targets contributing to disrupted innate immune response and contributing to subsequent inflammaging [30]. Defects in the migration and functions of macrophages and dendritic cells (DC) have been reported with aging [38, 53, 64–66]. Also noted are altered DC maturation [67] and cross-talk with T cells [68] that contribute to loss of antigenic tolerance with aging [69]. Related to these important innate immune functions, autophagy that regulates phagocytosis, modulates inflammasome function, and controls cytokine/chemokine production [70], is reduced, while proinflammatory cytokine responses are significantly increased. Aging is also associated with altered pattern recognition receptors (PRR) expression and signaling within innate immune cells [53] [71, 72], with Toll-like receptor (TLR)-dependent expression of costimulatory molecules also blunted in monocytes from older individuals [73, 74]. With aging there also appears to be an altered balance of natural killer (NK) cell subsets, with cytotoxic population functions being decreased [53, 75]; however, minimal information is available regarding this innate immune cell population with aging and periodontitis.

Overall, these findings generated a concept of poor innate immune responses in aging due to altered PRR actions leading to ineffective clearance of deleterious microbial stimuli that would prolong the duration of their activation and contributes to perpetuation of deleterious inflammatory responses with aging, although data are generally lacking on classes of PRR

beyond alteration in TLRs [76]. While many studies of innate immune functions have focused on professional immune cells, early studies of aging-related oral innate immune responses had an emphasis on resident epithelial cells and gingival fibroblasts. The results reinforced the hypothesis that age-related changes in the ability of gingival cells to respond to bacterial challenges and orchestrate tissue repair could be involved in a higher risk of periodontitis with aging [77–80].

Recently, we have used the nonhuman primate (rhesus) model of periodontal infection and inflammation [81–84] to document the aging-associated gingival transcriptome changes of different innate immune response pathways. The transcriptome of aged gingival tissues in nonhuman primates exhibited significant differences in innate immune pathways that are critical for maintaining a symbiotic relationship with the oral microbiome, and could predispose to microbial dysbiosis and periodontitis (Supplemental Figure 2). In particular, aging seems to enhance an anaerobic gingival environment coupled with an ability of gingival tissues/cells to sense and respond to microbes (in particular invasive pathogens) that appears to be critically compromised with aging. It is unclear at this point if these changes are related with a specific cell types (epithelial cells, fibroblasts, immune cells) or is a general characteristic for the entire periodontium.

Aging and Adaptive Immune Responses

An extensive literature supports that adaptive immune capabilities are dysregulated in aging, including T cells, B cells, and antigen-presenting cells [3, 53, 85–87] contributing to immunosenescence (Supplemental Figure 1). The adaptive immune system with its specificity derived from a broad diversity of antigen receptors is highly regulated regarding the cellular interactions engaging specific antigen receptors, cellular activation, and molecular effector functions of cells and biomolecules. Boraschi et al. [88] recently summarized potential causes of immunosenescence in the context of innovative strategies to counteract the decline of immune responsiveness with aging. However, we have a rather limited understanding of how aging affects: (i) the adaptive immune system responses to the bacteria that chronically colonize the oral cavity prior to disease, and (ii) how the magnitude and specificity of the response interfaces with pathogens that emerge within the oral bacterial ecology during exacerbations of disease.

The adaptive immune system is equipped with two key features: a diverse antigen recognition capacity by lymphocyte populations (naïve lymphocytes) and very long-lived antigen-experienced lymphocytes (memory lymphocytes). If the innate immune system is unsuccessful in eliminating the stimulus or stressor that is antigenic, it induces and recruits cells of the adaptive immune response (Supplemental Figure 3). Thus, a principal alteration responsible for immunosenescence is the overall decline of antigen-specific immunity due to a loss of numbers of naïve and regulatory T lymphocytes [29, 89–91] and reduced generation of progenitor B cells in the bone marrow [90, 92]. T cells from aged individuals display decreased T cell receptor (TCR) stimulation [93, 94], and altered cytokine profiles that reduce B cell helper functions [94]. Numerous alterations in B cells occur with aging [95] including differences in lymphocyte subpopulations [96, 97] and altered B-cell diversity [98] that would revise the antibody repertoire via reduced crucial rearrangement of variable

(V), diversity (D) and joining (J) gene segments [V(D)J] through recombination events and diminished effector antibody repertoires [95, 99–102]. Together these changes result in an age-dependent decrease in the diversity of both the T and B cell antigen-recognition repertoire.

In aged periodontal lesions the data suggest that aging-induced narrowing and skewing of both the T and B cell repertoire and diversity occurs in chronic periodontal diseases [13, 103, 104]. However, a summation of the available literature from human studies regarding aging effects on humoral immune responses to oral microorganisms provides rather minimal evidence to either support or refute that aging directly impacts the capacity of individuals to mount an adaptive immune response to bacteria comprising the autochthonous oral microbiome including those associated with periodontitis. Our recent studies indicated that aging had a minimal effect on overall antibody levels to the range of oral bacteria that were tested, when patients were stratified based upon the condition of the periodontium [105]. While antibody levels within age categories demonstrated positive correlations of the antibody to the oral pathogens in the younger group of individuals, with severe disease in older individuals greater clinical disease was associated with lower antibody to the oral pathogens. Thus, although the humoral adaptive immune response clearly changes from gingival health to periodontal diseases [19, 106], a conundrum exists of why there is a coincidence of chronic oral infection driving intervals of exacerbated disease and a generally substantial specific local and systemic immune response [13, 19]. In this regard, a pathogen strategy for host evasion has been described as antigenic variation, antigenic drift, and antigenic diversity depending upon the pathogenic species [107–118]. The lack of clear “immunity” in periodontal diseases may be related to this antigenic drift and diversity in the oral opportunistic pathogens that chronically colonize and are subject to host immune pressure, leading to a selective advantage that accompanies antigenic alterations of the bacteria within the subgingival ecology. We implemented a study to examine the concept that *P. gingivalis*, as an opportunistic pathogen, demonstrates characteristics of antigenic diversity/drift that in susceptible hosts would favor maintenance of its colonization and the capacity of clonal genetic diversity to enable emergence to threshold levels triggering disease episode exacerbations [119–122]. Our results suggested that *P. gingivalis* has the ability to alter expression of potentially critical antigens [123] reflected in a unique antigenic portfolio expressed by various *P. gingivalis* strains consistent with antigenic diversity and drift (Figure 3A). Moreover, we observed that aging decreased the antibody to the array of *P. gingivalis* strains that appeared to reflect a more limited repertoire of antibody to the range of *P. gingivalis* antigens. One interpretation of these findings would be that while overall antibody levels were not affected by aging, the quality of the response at the individual level was not adequate to manage the chronic infection enabling more frequent/extended episodes of active disease. Sorting out this host-microbe relationship and understanding if this feature is being driven by targeted antigenic changes in the pathogen, or altered capacity of the host immune system to control the chronic infection is an important facet of future approaches to improved precision in periodontal diagnosis and therapy [52, 124, 125].

We have also evaluated various aspects of gene expression that would contribute to adaptive immune responses in gingival tissues using a nonhuman primate model of periodontitis, including antigen presenting cells [126–128], characteristics of macrophage footprints in

healthy and periodontitis gingival tissues from animals across their lifespan and plasticity of the macrophage population in gingival tissues [129], T cell phenotype/function during the initiation and progression of periodontitis [130], and B cell and plasmacyte responses activities in healthy tissues potentially contributing to muting the effects of the tissue destructive biomolecules, whereas with aging and periodontitis this relationship is adversely affected and may enable a progression of tissue destructive events (##) (Supplemental Figure 2).

Aging and Osteoimmunology

Numerous immune and non-immune cells within the periodontium communicate with both osteoblasts and osteoclasts modulating the balance of physiologic bone formation and resorption [131, 132]. Similarly, advances in the field of osteoimmunology clearly show that cytokines produced as a result of the associated innate and adaptive host response also contribute to the disruption of local bone homeostasis and osteoclastogenesis [133]. Therefore, age-related alterations in the function of both innate and adaptive immune cells would be expected to directly affect bone metabolism and remodeling involved in periodontal diseases. Using the nonhuman primate model we generated data that suggested a gingival transcriptome environment that reflects a more general osteogenic homeostasis in aging healthy tissues with the potential to regulate osteoclast and osteoblast functions to help control inappropriate microbial stimulation from the accretion of oral biofilms. Alterations in gene expression in periodontitis particularly in aged animals were skewed towards creating an environment with substantial osteoclastogenic potential consistent with the bone resorption in periodontitis (Supplemental Figure 2). These data indicated that local bone resorptive processes are up-regulated under the condition of aging creating a tissue destructive environment [134]. More recently, we evaluated the potential interaction between human antibody responses to *P. gingivalis* and activation of osteoclasts (OC) as an entry point into more critical definition of how these antibodies might function in health and disease. Our findings showed significant reduction of osteoclastogenesis by the pathogen following opsonization with human antibody. Furthermore, opsonized bacteria transformed OC precursors to a “macrophage phenotype” suggesting a bone protective role of the immune complexes in modulating osteoclastogenesis [135]. Further defining effective antibody isotypes, avidity, and antigenic specificity as related to increased disease and altered immune responses in aging could improve targets for eliciting protective immunity.

The Exposome and Nutritional Immunology of Aging and Periodontitis

Despite increasing awareness and improvement in oral health, periodontitis remains a major health concern across the lifespan in the United States [136–139]. Similar to many chronic diseases, it is well documented that periodontal diseases are complex with multiple potential contributing factors including genetic and epigenetic influences, patient behaviors, medication use, and/or environmental factors, which combine to promote disease initiation and progression [140]. Studies from other disease models show that various extrinsic environmental stimuli can contribute to biologic and epigenetic changes that underpin the concept of environment-gene interactions related to disease expression [141]. However, limited data is available regarding the environmental risk factors in periodontitis [142],

therefore, we conducted an associational study with periodontitis in the U.S. adult population using NHANES data with measures of 156 environmental factors (ie. exposome) that could be a direct contributor to the microbial dysbiosis [143] and/or a modifier of host responses through altered molecular pathways or modulation of genetic control of the disease [144, 145]. Our findings identified more classical factors (*i.e.* age, gender, race/ethnicity) in the disease model, but for the first time integrated a subset of environmental factors, both toxins (eg. lead, hydrocarbons, polychlorinated biphenyls) and blood nutrients (eg. carotenoids, Vitamin D, folate, and Vitamin E) that appear to substantially modify the prevalence of periodontitis in the population [146–151] (Figure 3B). Moreover, dietary polyphenols in a wide range of foods have also been shown to function via anti-inflammatory and antioxidant mechanisms [152], thus having the potential to impact various mechanisms to reduce the initiation and progression of periodontitis. Observational studies have likewise attributed effects of the intake of antioxidant nutrient containing fruits and vegetables for reducing oxidative stress and inflammation [153–155], including periodontitis [156]. Thus, a combination of various environmental stressors altering fundamental balances in host cell functions that may already be stressed by a dysbiotic microbiome presents a new consideration regarding environment-gene interactions and expression of periodontitis particularly as related to aging processes. The nutrients and dietary bioactive compounds could be evaluated in future prospective studies, to delineate causal linkages in protection against the development of periodontitis. Delivery of an optimized combination of these nutrients at each meal or via snacks, in combination with adequate measures of standard oral hygiene care may provide evidence for an effective therapy in the prevention of periodontitis.

Concluding Remarks

The aging process clearly contributes to the incidence and severity of periodontitis [51, 52, 157, 158] and has been related to altered physiologic and pathophysiologic changes enabling a dysregulation of normal development, maturation, replenishment, and response patterns of the immune system to the noxious challenge of the disease-associated oral microbiome [159]. A detailed understanding of the molecular mechanisms and pathways that control normal versus abnormal responses in aging that could contribute to expression of periodontal diseases would be of great benefit within the context of the aging U.S. population. Nevertheless, a fundamental gap remains in our elucidation of the breadth and depth of aging effects on the phenotypic response profiles to the oral microbiome, and in particular pathogens that emerge with disease. How the specific responses are modulated by the bacteria, and subsequently modulate the bacterial biofilms remains undetermined. Furthermore, how/if critical bacteria contributing to the disease process diversify their antigenic characteristics to ultimately “evade” host responses and enable emergence in biofilms to threshold levels driving tissue destructive events has not been demonstrated. This report attempts to provide an overview of the various alterations in the host response armamentarium that is affected with aging. However, a critical facet of the existing literature of aging processes is focused on the relationship of chronological age with disease and host responses. Nevertheless it is very clear that across the human population there is extensive variation in aging effects that generally reflect a composite of genetics and environmental

exposures [160]. This variation has engendered discussion of the concept of “biological aging” [160–165], encompassing strategies to develop anti-aging (“geroprotective”) or senolytic (kill senescent cells) therapeutics to slow the aging processes and/or enhance healthy biologic aging [166–171].

In contrast to these approaches to positively impact aging processes through diet, novel pharmaceuticals, and behavioral strategies, we would like to propose the concept of “gerovulnerability”. This model emphasizes the clear individual differences within the population related to the onset and progression of aging processes. It also stresses important fundamental differences in chronological versus biologic aging at the individual level. The actual cause(s) of immunosenescence and “inflammaging” remain to be established [2, 87]. Aging effects on the immune system include distinct alterations in both innate and adaptive immune cell functions and effector biomolecules contributing to processes of immunosenescence, immunoactivation, and inflammaging. Furthermore, aging associated *in vivo* microenvironments, such as a chronically inflamed periodontium, likely also contribute to the complexity of these aging defects. The heightened inflammation observed in the periodontium of aged individuals reflecting an ineffective immunity leads to chronic persistence of these pathogens and unresolved destructive inflammation with contributions from both arms of immunity [36]. Nevertheless there is clearly an array of systemic health conditions related to bacterial translocation through damaged periodontal tissues and the resulting chronic elevation in systemic inflammatory responses that leverage with other risk factors for general disease processes [41, 172]. Byerley et al [173] have described a serum profile that represents healthy aging, coupled with additional studies describing the concept of specific metabolic and genetic/epigenetic markers of biological age [174–177], and linked with previous descriptions of telomere shortening [161] and genes controlling the aging process [178]. Interestingly, Kim and Jazwinski [179] provided a recent report suggesting that the characteristics of the gut microbiome contribute directly to healthy or unhealthy aging, albeit similar exploration of existing data has not been provided related to the oral microbiome effects on these processes. Thus, a number of studies have begun to focus on arrays of measures that could explain and/or predict biological aging and model the rate of senescence to predict mortality [160, 163, 165, 180]. It is conceivable that chronic periodontitis existing over decades in an individual, with onset in some individuals by the 3rd decade of life could be an important comorbid condition contributing to “gerovulnerability” and unhealthy aging. Thus, our preliminary recent results derived from NHANES data (1999–2002) suggesting decreased telomere base pairs with periodontitis (Figure 3C), indicates that rather than simply limiting our perspective to aging processes generating an environment enabling a greater prevalence/extent of periodontitis [165], this chronic infection and persistent local and systemic inflammation may help drive an unhealthy aging progression. Despite the challenges of aging and periodontal research, it is crucial to understand the mechanisms responsible for age-related changes in the immune system in order to develop strategies to maintain good health in the aging population, which will clearly have a major impact on influencing the future of prevention, management, and interventional clinical decisions and implementation for the dental profession [52].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Schematic of interactions of genetics and host responses that contribute to age-associated diseases (originally published in [159]).

Figure 2:

Schematic of the host-microbe interactions in periodontitis. Includes identification of both modifiable (eg. smoking, diabetes, etc.) and non-modifiable (eg. sex, race/ethnicity, age) factors that could modulate the oral microbiome and host response to the microbiome components. Also, of note is the potential that aging substantively affects the modifiable components, as well as the composite interactions of aging in controlling responses and disease expression related to sex and race/ethnicity across the population (modified from [159]).

Figure 3:

(A) Proposed antigenic diversity of *P. gingivalis* within the human population, reflected by individual differences in antibody response profiles to specific *P. gingivalis* strains. Additionally, the impact of age (in years) on these response patterns is shown. The bars denote group means from ≤35 years (n=87), 36–50 years (n=151) and >50 years (n=58) subjects and the vertical practice describe 1 SEM for the groups. The lines denote significant differences at $p<0.05$. The *P. gingivalis* strains are: ATCC33277, FCD381, W50, W83, A7A1–28, and A7436. (B) Levels of selected nutrients in blood of subjects >65 years of age derived from the NHANES 1999–2004 dataset. Periodontitis was defined as a site with clinical attachment loss (CAL) ≥3 mm and a periodontal pocket ≥4 mm. NHANES (1999–2004) used the partial-mouth periodontal examination protocol to sample teeth and sites [181–183]. The protocols randomly selected two quadrants of the mouth and specified 2 to 3 sites per tooth for measurement of pocket depth, attachment loss, and bleed on probing. In

1999–2000, two sites per tooth (mid-facial and mesio-facial) were measured, while three sites per tooth (mid-facial, mesio-facial and distal) were measured in 2001–2002 and 2003–2004. The bars denote group means [Normal (no periodontitis), n=1019–1453; Perio, n=133–220] and the vertical brackets enclose 1 SEM. The asterisk (*) denote significant differences at $p<0.05$. (C) Measured telomere length compared to standard reference DNA [Mean telomere length relative to standard reference DNA (T/S) ratio; https://wwwn.cdc.gov/Nchs/Nhanes/2001-2002/TELO_B.htm]. The points denote group mean levels and the vertical brackets enclose 1 SEM. The asterisk (*) denote significant differences at $p<0.05$.