The Potential Lifespan Impact of Gingivitis and Periodontitis in Children

Bimstein E* / Huja PE** / Ebersole JL***

The prevalence of gingivitis in children can be similar to or greater than dental caries, but has received much less attention in understanding the long-term impact on overall health. Oral health providers must take into consideration that the clinical presentation of the gingivitis progression/severity in the primary dentition is only evident when the magnitude of the inflammatory cell infiltrate approximates the gingival surface reflected by inflamed tissues. Moreover, despite its relatively benign clinical appearance, the establishment of chronic inflammation of the periodontal tissues in childhood may have the potential for local tissue destruction leading to periodontitis, and/or create an "at-risk" environment in the tissues that could adversely affect the health of these tissues across the lifespan. The present manuscript presents some fundamental information regarding the characteristics of chronic inflammation in gingival tissues of children and adolescents and speculates about the lifetime impact of gingival and periodontal infections in childhood on future oral and systemic health in the adult.

***Keywords**: Gingivitis, periodontitis, children, potential impact*

INTRODUCTION

The AAPD states that "The scope of pediatric dentistry includes an age-defined specialty that provides both primary and comprehensive preventive and therapeutic oral health care for infants, and children through adolescence".[1] Nevertheless, while a substantial amount of attention has been placed on the features of early childhood caries, relatively less attention has been placed on gingival inflammation (*ie.* gingivitis) elicited by a very different group of bacteria, which is also an early–life oral infection. This disease may be equally or more prevalent than caries and has the potential of affecting thousands of children and young adolescents.[2-4] As importantly, this early infection may facilitate a gingival environment that can presage the establishment of periodontitis, which is the primary reason of tooth loss in adulthood.[5,6] The purpose of the present review is to emphasize that gingival inflammation is a clinical manifestation of the most common infectious disease in children and that if neglected, could contribute to long-term detrimental oral and systemic health outcomes.

* Enrique Bimstein, CD, Professor of Pediatric Dentistry, Chief of the Division Pediatric Dentistry.

** Pinar Emecen Huja, DDS, PhD, Assistant Professor, Division of Periodontics.

*** Jeffrey L Ebersole, BS, PhD,Professor of Oral Health Research, Associate Dean and Director of the Center of Oral Health Research.

Send all correspondence to: Enrique Bimstein, UK College of Dentistry, D-418, Lexington, KY, 40503-6261

Tel: 859 323 5388
Fax: 859 323 4685

E-mail: ebi223@uky.edu

Prevalence of caries and gingival/periodontal diseases in children and adolescents

The Centers for Disease Control and Prevention state that "Although dental caries is largely preventable, it remains the most common chronic disease of children aged 6 to 11 years (25%), and adolescents aged 12 to 19 years (59%).[7] Accordingly, the American Academy of Pediatrics states that "Dental caries has been reported by the Centers for Disease Control and Prevention to be perhaps the most prevalent infectious disease of our nation's children" and the American Academy of Pediatric Dentistry (AAPD) indicates that dental caries and its sequelae are among the most prevalent health problems facing infants, children, and adolescents in America.[8, 9]

The AAPD also states that "Gingivitis is nearly universal in children and adolescents, it usually responds to thorough removal of bacterial deposits and improved oral hygiene and that self-administered plaque control programs without periodic professional reinforcement are inconsistent in providing long-term inhibition of gingivitis".[9] Thus, it has been clearly demonstrated that plaque-induced gingivitis is prevalent at all ages of the dentate population,[10-12] and that it is the most common and prevalent disease form of the periodontium among children and adolescents. Moreover, the severity and prevalence of gingivitis will progressively intensify from the primary through the permanent dentition;[13-16] the incidence and severity of gingivitis increase from childhood to adolescence, reaching a peak prevalence of 80% at 11– 13 years of age.[4] Thereafter, the severity of gingivitis declines, albeit chronic periodontitis defined by periodontal tissue attachment loss and alveolar bone resorption increases in prevalence and severity with age.[17]

Clinical features of gingivitis in children and adolescents

The development of pathological outcomes that can be expressed as the incidence and severity of clinical manifestations of gingivitis and

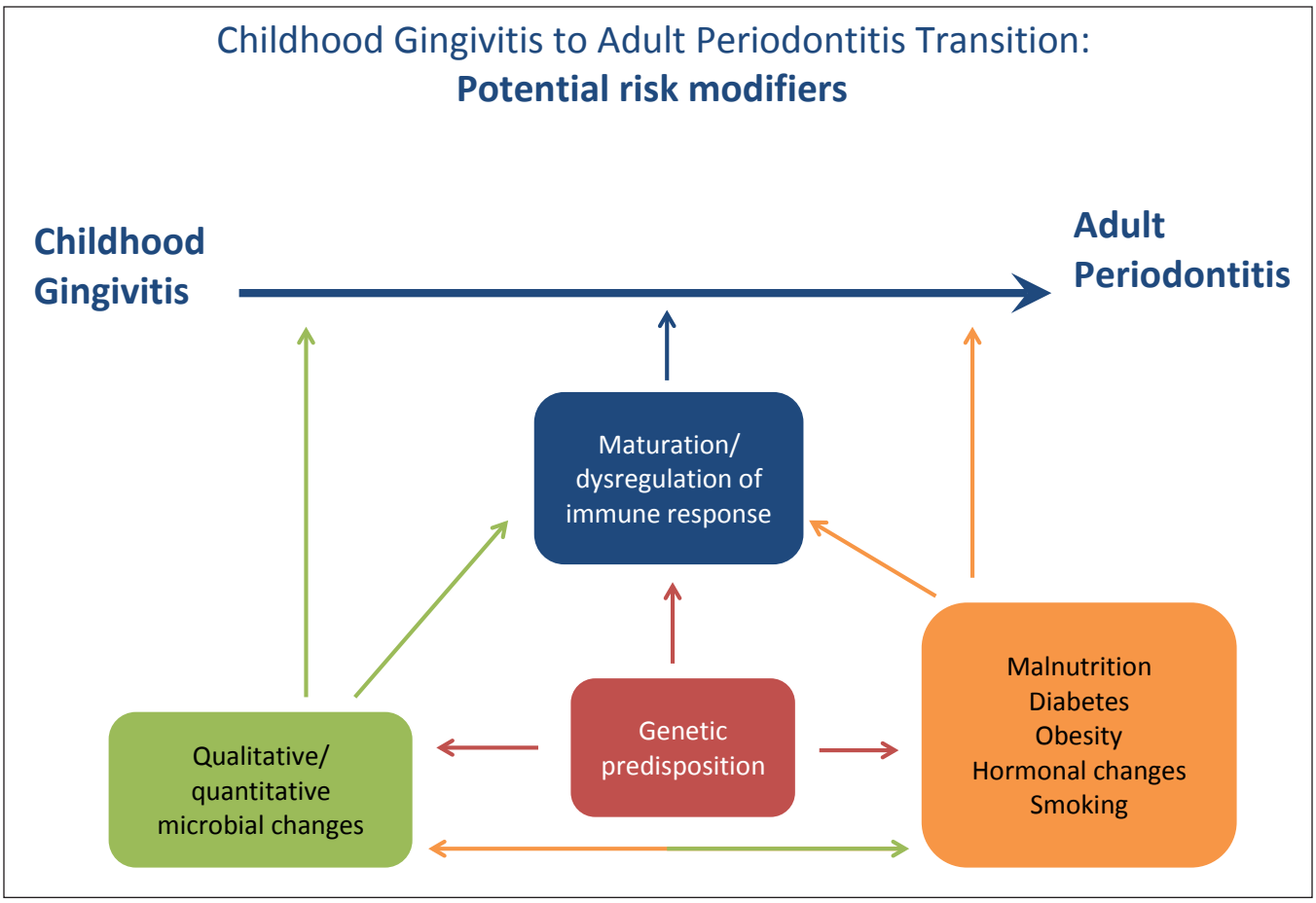

Figure 1. Diagrammatic representation of the potential risk modifiers involved in the transition from childhood gingivitis to periodontitis.

periodontitis, reflect host-bacterial interactions in the periodontium. These clinical phenotypes are based upon a variety of biological changes in the gingival and periodontal structures, the character of formation/organization/maturation of supra- and subgingival dental biofilms, and the development and impact of the immune system over the lifespan.[18-20]

The reasons for the diminished attention to gingivitis in the primary dentition, when compared to the emphasis placed on dental caries, may include that in children the clinical image of carious lesions is much more dramatic than the one for gingival inflammation. Additionally, once an open carious lesion has been established it cannot be reversed, while immediate clinical features of gingivitis are generally easily reversed with appropriate oral hygiene. In most cases, the clinical evidence of gingival inflammation and periodontitis in children may vary and the response judged benign; however, the innocent appearance of gingivitis in children should not be underestimated. The initial stages of gingivitis in the primary dentition are not clinically detectable, since the inflammatory infiltrate is masked by the overlying gingival tissues. When the extent of the inflammatory cell infiltrate increases in magnitude and subsequently approximates the gingival tissue surface, the clinical redness and edema then correlates positively with the presence of the inflammatory infiltrate within the tissues, reaching a zenith at puberty.[10, 16, 21-24]

Oral health providers must also be aware that there is an age dependent inflammatory reaction of the gingival tissues that has been related to changes in the qualitative and quantitative bacterial composition of the dental biofilms, the maturation of immune responses, hormonal changes, morphological differences in the periodontium, and tooth eruption and shedding.[15] Subsequent changes in microbial plaque composition and load, and food debris accumulation resulting from carious lesions may further boost deterioration of the gingival conditions and contribute to the development of further destructive processes in the periodontium (Figure 1).[25]

Biology of Gingivitis and Periodontitis in Children and Adolescents

With the evolution of the Human Microbiome Project (HMP) in concert with the completed Human Genome Project (HGP), we must now look differently at the interaction between the microbes and host interactions needed to maintain health, or are deregulated resulting in disease.[26,27] The HGP provided a map of the human genome, completed in 2003, but followed over the last decade with increasingly sophisticated studies of "functional genomics" to help identify how expression of an individual's genome sequence was critical to the variations in health and disease across the population.[28] Evidence from the HMP has provided some interesting new findings and concepts regarding the role of the human microbiome in health and disease. In some way this is based on the estimate that for every human cell in our body, there are 10 bacterial cells that colonize the body and must contribute towards health and disease in ways not previously considered. Within the HMP, multiple oral sites were sampled and the oral microbiome is being catalogued.[29,30] While

this catalogue has yet to be used very effectively as a roadmap for improving oral health, striking conclusions have arisen from studies of the gut microbiome.[31-33] A rapidly expanding literature in this area has demonstrated dramatic effects on developmental characteristics of general host immune and inflammatory responses. Some elaboration of these approaches related to oral health in children and adolescents is provided in the following section.

Host Responses

The immune responses can be divided into innate (non-specific) and adaptive (specific) responses: the innate responses are the first line of defense and present the advantage of an immediate reaction against an infectious challenge involving inflammatory reactions, and the adaptive responses are generally more specific for infectious agents or other antigens, and therefore more effective.[34] However, this system lacks memory and specificity, and may result in collateral host tissue damage. In periodontal diseases, the innate response system can be described as: (i) the intact gingival sulcular and junctional epithelium act as a barrier against bacterial products; (ii) saliva and gingival crevicular fluid provides a continuous flushing of the oral mucosal surfaces and deliver antimicrobial biomolecules; (iii) the normal commensal microbiota of the mouth inhibit colonization/growth/emergence of pathogenic microorganisms in the oral ecology; and (iv) phagocytic cells migrate into the gingival tissues from the vasculature, including polymorphonuclear leukocytes (neutrophils), monocyte/macrophages, and natural killer cells that are capable of directly destroying infectious agents.[35]

Inflammatory processes that initiate gingivitis are an early step required to initiate broader immune responses and share many cellular and molecular factors with the innate immune system.[35,36] Although inflammation and innate immunity are considered non-specific forms of the host response to microbial challenges, they manifest as organized responses that are coordinated through a wide range of cellular receptors like Toll-like receptors (TLR), soluble molecules (*e.g.* CD14) and various microbial ligands, pathogen-associated molecular patterns (PAMPs), microbial associated molecular patterns (MAMPs) and danger-associated molecular patterns (DAMPs).[37,38] The interactions between infectious agents and these host proteins stimulate production and secretion of inflammatory mediators.[39] Generally, the literature suggests that these responses have less intensity to Gram-positive bacteria compared to Gram-negative bacteria using *in vitro* assays, albeit, host cells have receptors for molecules from both morphotypes of bacteria.[39] Gingivitis is characterized by a primary vascular response to non-specific bacterial accumulation leading to increased vascular permeability, leakage of plasma into the tissues, and an inflammatory cell infiltrate. Yet, some studies have documented the presence of specific antibodies to putative periodontopathogens, *ie. P. gingivalis, Aggregatibacter actinomycetemcomitans* in patients with gingivitis,[40] different levels of IgM antibody have been found in children with gingivitis when compared to adults, and IgG levels in children have been found to be helpful to distinguish between sites with and without gingivitis in children whereas IgG levels were detected unrelated to gingivitis in adults.[41]

When the innate and inflammatory responses are insufficient to eliminate the noxious challenge of the infectious agent, adaptive responses that consist a specific second line of defense are activated.[35] While innate and adaptive response mechanisms share similarities in cells and signaling molecules, adaptive responses are specifically related to specialized functions of lymphocytes, including T and B lymphocytes. Generally healthy gingival tissue have few mononuclear cells present, albeit, the presence of bacteria juxtaposed to the epithelial tissues does elicit subclinical histological inflammation with some neutrophils detected. Accumulation of bacteria at the gingival margin elicits increased clinical inflammation, *ie.* gingivitis, accompanied by increases in the tissue and crevicular neutrophils numbers and increases in T cell numbers.[22] Generally these T cells show a distribution of CD4/CD8 ratios similar to blood and are suggested to represent a more regulatory T cell phenotype attempting to reestablish homeostasis in the tissues.[42] However, long standing gingivitis is reflected by increasing numbers and types of T cells, as well as an influx of some B cells into the inflamed tissues, seemingly preparing the environment for an adaptive immune response; as such, the mononuclear cell composition of periodontitis lesions has been described as enriched for plasma cells and B cells, with the proportion of B cells greater than T cells in established lesions.[22] The literature remains somewhat controversial regarding relative levels and functions of T helper cells versus T cytotoxic cells in the lesions,[42-44] It also has been emphasized that lesions from aggressive and chronic periodontitis present similar cell compositions and generally similar molecular signatures.[45]

Aggressive periodontitis (AgP) is a special form of periodontitis observed in children and adolescents.[46-50] The prevalence of AgP in these populations has been described to be from 0.5 to 2% dependent upon the target population; with higher incidence in populations with African heritage.[46] It is mostly characterized by onset at an early age (at the early primary dentition or circumpubertal), rapid bone destruction, and a history of familial involvement.[47-48] A recent study investigating pathogenesis of localized aggressive periodontitis detected an increased inflammatory 'hyper-responsive trait upon stimulation of innate immune receptors with lipopolysaccharide of *E. coli* and *P. gingivalis* in aggressive periodontitis patients, when compared to healthy siblings and unrelated healthy controls.[49] A continuation of this study reported the presence of systemic hyper-inflammatory responses in patients with localized aggressive periodontitis.[51] Thus, it was suggested that in this subset of periodontitis susceptible patients a localized inflammation can initiate a local destruction and result in production of systemic immune activating agents. This leads to perpetuation of inflammatory cycle where excessive and rapid local tissue destruction is observed.[50]

The level of molecular data on the inflammatory response in gingivitis tissues/fluids is still somewhat sparse and primarily limited to naturally occurring or experimental gingivitis in adults. Furthermore, little data is available regarding the changes in gene expression and biomolecule production that accompanies this inflammation in the general adolescent or children population. Thus, a substantial gap in our knowledge remains regarding these responses and how they interact with the biofilm accretion in younger individuals.

Lifespan Impact of Chronic Oral Infections of Children and Adolescents

The underlying rationale for clinical management of periodontal diseases is to physically and/or chemically interfere with the microbial accumulation that triggers the inflammatory responses in the gingival tissues.[22,35] While not absolute, it is generally accepted that reversible gingivitis precedes periodontitis, and lacking intervention

to limit bacterial accumulation and biofilm maturation the gingival lesion can progress to involve deeper parts of the periodontium resulting in loss of soft tissue and hard tissue functions.[22,35] Therefore, a primary approach to preventing the development of periodontitis is to control gingivitis. [5,18]

Due to the age-dependent reaction of the gingival tissues to oral bacteria, infants and small children tend to exhibit attenuated clinical signs of gingival inflammation even in the presence of a substantive microbial burden.[13-15, 25, 51] Thus, an increased susceptibility to subsequent gingival and periodontal diseases should be suspected when a child presents severe gingival inflammation, especially if the severity of the gingival inflammation does not appear to be proportional to dental plaque accumulation. While this increased risk for future disease may reflect some enhanced pathogenic properties of the existing oral microbiota, the clinical observations could also indicate a genetic predisposition to deregulated inflammatory responses, or even immune system abnormalities related to systemic diseases, such as malnutrition, diabetes or more serious diseases such as leukemia or HIV infection.

As importantly, the available literature does not strongly support that periodontal pathogens that contribute to the etiology of periodontitis in adults are acquired later in life (*eg.* after 35 years of age), when the disease is manifest. In fact, similar to the literature on *Streptococcus mutans* and dental caries, it appears that these potential pathogens are acquired early in life and establish themselves at low levels in the oral microbiome of the child/adolescent. Once the individual's autochthonous oral microbial ecology is established, it appears quite difficult for extrinsic bacteria to acquire a foothold for permanent colonization. What appears to occur is that changes in the oral environment contribute to selecting for the emergence of various taxa, genera, and species that can trigger a disease process. Thus, there remains a substantial gap in our understanding at the molecular level of the existence of potential pathogens in the oral ecology of children with detectable specific immune responses, clinical presentation of gingival inflammation, and a general lack of progression to irreversible destructive disease in younger individuals. However, based upon current epidemiologic evidence it could be expected that 60-70% of these children will develop periodontitis later in life, presumably related to acquisition of a "risk microbial ecology" at an early age. Consequently, the concept that gingivitis in children and adolescents is an aesthetic issue that can easily be controlled by professional mechanical therapy may be underestimating the longer-term implication in individuals with frequent, severe, and/or chronic episodes of gingivitis.

It is clear in adults that breakdown of the integrity of the periodontal tissues enhances the distribution of oral microorganisms into the systemic circulation, potentially transmitting oral bacteria to distant tissues (*Porphyromonas gingivalis* in atheroma, *Fusobacterium nucleatum* in placenta, oral bacteria in arthritic joints). Recent data from adults that link obesity with periodontitis and systemic diseases could be extrapolated to the increasing burden of obesity in children and adolescents and the capacity of this increased adipose tissue to create a systemic inflammatory environment.[52, 53] Thus, it might be expected that in obese, and even overweight, children and adolescents, these altered systemic response parameters may be reflected in the gingival tissues early in life and "seed" a long-term enhanced risk for destruction of the periodontal tissues. Thus, initiating the translocation of oral bacteria to a systemic challenge at a younger age could have long-term consequences.[34] Consequently, these chronic oral infections in children coupled with obesity and altered systemic health could have a substantial cumulative effect on cardiovascular disease, onset of diabetes, and other disease risks of chronic inflammation.

CONCLUSION

This review suggests that a more robust multidisciplinary approach is required to evaluate the short and long-term impact of gingival inflammation in children and adolescents. A clearer understanding of individual responses to standard prevention and treatment approaches needs to be developed. Moreover, investigation of gingival and periodontal diseases in children and adolescents should incorporate a broader view of the role of variations in the oral microbiome throughout the life of the individual patient. Couple this with molecular variations in age dependent gingival inflammatory responses to these oral microbial biofilms, will enable a better understanding of the individual's potential for future destructive oral disease and the associated risk for systemic sequelae later in life.

REFERENCES

1. American Academy of Pediatric Dentistry, Pediatric Dentistry Reference Manual. Overview, definitions and scope of Pediatric dentistry. *Pediatr Dent, 34*: 2-3, 2012.
2. Nowzari H, Botero JE, Rich SK. The impact of early-in life periodontal infection on the smiles of children: a worldwide view. *Compend Contin Educ Dent, 31*: 154, 156-8, 160 passim, 2010.
3. Oh T-J, Eber R, Wang H-L: Periodontal diseases in the child and adolescent. *J Clin Periodontol, 29*: 400–10, 2002.
4. Dibart S. Children adolescents and periodontal disease. *J Dent, 25*: 79-89, 1997.
5. Albandar JM, Brunelle JA, Kingman A. Destructive periodontal disease in adults 30 years of age and older in the United States, 1988-1994. *J Periodontol, 70*: 13-29, 1999.
6. Montandon A, Zuza E, Toledo BE. Prevalence and reasons for tooth loss in a simple from a dental clinic in Brazil. *Int J Dent 2012* Available on line August 29 at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3437633/. Accessed August 15 2013.
7. Department of Health and Human Services, Centers for the Disease Control and Prevention. Available at: http://www.cdc.gov/oralhealth/publications/factsheets/dental_caries.htm. Accessed August 15, 2013.
8. American Academy of Pediatrics. Policy Statement. Section on Pediatric Dentistry. Oral health risk assessment timing and establishment of the dental home. *Pediatrics, 111*: 1113-6, 2003.
9. American Academy of Pediatric Dentistry, Pediatric Dentistry Reference Manual. Guideline on periodicity of examination, preventive dental services, anticipatory guidance/counseling. And oral treatments for infants, children and adolescents. *Pediatr Dent, 34*: 110-6, 2012.
10. Stamm JW. Epidemiology of gingivitis. J Clin Periodontol, 13: 360-6,1986.
11. Bhat M. Periodontal health of 14-17-years-old US schoolchildren. *J Pub Health, 51*: 5-11, 1991.
12. Page RC. Oral health status in the United States: prevalence of inflammatory periodontal diseases. *J Dent Educ, 49*: 354-64, 1985.
13. Mackler SB, Crawford JJ. Plaque development and gingivitis in the primary dentition. *J Periodontol , 44:* 18-24, 1973.
14. Matsson L. Development of gingivitis in the preschool children and young adults. *J Clin Periodontol , 5*: 24-34, 1978.
15. Bimstein E, Matsson L. Growth and development considerations in the diagnosis of gingivitis and periodontitis in children. *Pediatr Dent, 21*: 186-91, 1999.
16. Hugoson A. Koch G, Göthberg C, Helkimo AN, Lundin SA, Norderyd O, Sjödin B, Sondell K. Oral health of individuals aged 3-80 years in Jonkoping during 30 years (1973-2003). I. Review of findings on dental care habits and knowledge on health care habits and knowledge of oral health. *Swed Dent J, 29*: 125-38, 2005

17. Spencer AJ, Beighton D, Higgins T. Periodontal disease in five and six year old children. *J Periodontol, 54*: 19–22, 1983.
18. Löe H. principles of aetiology and pathogenesis governing the treatment of periodontal disease. *Int Dent J, 2*:119-26, 1983.
19. Brown LJ, Löe H. Prevalence, extent, severity and progression of periodontal disease. *Periodontol 2000, 2*:57–71, 1993.
20. Mariotti AJ. Gingival diseases. In: Bimstein E, Needleman HL, Karimbux N, Van Dyke TE, eds. Periodontal and gingival health and diseases. Children, adolescents and Young adults. Martin Dunitz Ltd, London; 31-48, 2001
21. Parfitt GJ. A five year longitudinal study of the gingival condition of a group of children in England. *J Periodontol, 28*: 26-32, 1957.
22. Page RC, Schroeder HE. Pathogenesis of inflammatory periodontal diseases. *Lab Invest, 33*: 235-49, 1976.
23. Bimstein E, Lustmann J, Soskolne WA. A clinical and histometric study of gingivitis associated with the human deciduous dentition. *J Periodontol, 56*: 293-6, 1985.
24. Bimstein E, Soskolne WA, Lustmann J, Gazit D, Bab I. Gingivitis in the human dentition. A correlative clinical and block surface light microscopic (BSLM) study. *J Clin Periodontol, 15*: 575-80, 1988.
25. Bimstein E, Garcia-Godoy F. The significance of age, proximal caries, gingival inflammation, probing depths and the loss of lamina dura in the diagnosis of alveolar bone loss in the primary molars. *ASDC J Dent Child 6*:125-8, 1994.
26. Turnbaugh PJ, Ley RE, Hamady M, Frase-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature, 449*: 804-10, 2007.
27. International Human genome sequencing consortium, Initial sequencing and analysis of the human genome. *Nature, 409*: 860-921, 2001.
28. Collins FS, Morgan M, Patrinos A. The human genome project: Lessons from large-scale biology. *Science, 300*: 286-90, 2003.
29. Chen T, Yu W-H, Izard O, Baranova OV, Lakshmanan A, Derwhirst FE. The human oral microbiome database: a web based accessible resource for investigating oral microbe taxonomic and genomic information. Available at: http://www.homd.org Database 2010;baq013 doi10.1093/databasebaq013. Accessed August 15, 2013.
30. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, Lakshmanan A, Wade WG. The human microbiome. *J Bacteriol, 192*:5002-17, 2010.
31. Devaraj S, Hemarajata P, Versalovic. The human gut microbiome and body metabolism: implications for obesity and diabetes. *Clin Chem, 59*: 617-28, 2013.
32. Pimentel GD, Micheletti TO, Pace F, Rosa JC, Santos RVT, Sira FS. Gut-central nervous system axis is a target for nutritional therapies. *Nutr J, 10*;11:22. doi: 10.1186/1475-2891-11-22, Available at http://www.ncbi.nlm.nih.gov/pubmed/22490672. Accessed on August 15, 2013.
33. Berer K, Khrisnamoorthy G. Commensal gut flora and brain autoimmunity: a love or hate affair? *Acta Neuropathol, 125*: 639-51, 2012.
34. Schenkein HA. Pathogenesis of aggressive periodontitis. In: Bimstein E, Needleman HL, Karimbux N, Van Dyke TE, eds. Periodontal and gingival health and diseases. Children, adolescents and young adults. Martin Dunitz, Ltd. London; 147-67, 2001.
35. Kinane FD, Berglundh T, Lindhe J. Pathogenesis of periodontitis. In: Lindhe J, Lang NP, Karring T, eds. Clinical Periodontology and Implant dentistry, 5th Edition. Blackwell publishing, Iowa; 285-306, 2008.
36. Berglundh T, Liljenberg B, Lindhe J. Some cytokine profiles of T-helper cells in lesions of advanced periodontitis. *J Clin Periodontol, 29*: 705-9, 2002.
37. Tietze K, Dalpke A, Morath S, Mutters R, Heeg K, Nonnenmacher C. Differences in innate immune responses upon stimulation of gram- positive and gram- negative bacteria. *J Periodon Res, 41*:447-54, 2006.
38. Hagishengalis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model for periodontal disease etiology. *Mol Oral Microbiol, 27*: 409-19, 2012.
39. Peyyala R, Kirakodu SS, Novak KF, Ebersole JL. Oral microbial biofilm stimulation of epithelial cell response. *Cytokine, 58*: 67-72, 2012.
40. Nakagawa, T. Nakagawa, S. Ishihara, K. Yamada, S. Machida, Y., Okuda, K. Reactive antibodies in sera from pubertal and adult gingivitis patients against various Porphyromonas gingivalis antigens. *J Periodontal Res, 30*: 396-403, 1995.
41. Bimstein E, Ebersole JL. Serum antibody levels to oral microorganisms in children and young adults with relation to severity of gingival disease. *Pediatr Dent, 13*: 267-72, 1991.
42. Ohlrich RJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. *Aust Dent J, 54*(Suppl 1):S2-10, 2009.
43. Teng T-YA, The role of acquired immunity and periodontal disease progression. *Crit Rev Oral Biol and Med, 14*: 237-52, 2003.
44. Berglundh T and Donati M. Aspects of adaptive host response in periodontitis. *J Clin Periodontol, 32*(suppl6): 87-107, 2005.
45. Papapanou PN, Abron A, Verbitsky M, Picolos D, Yang J, Qin J, Fine JB, Pavdilis P. Gene expression signatures on chronic and aggressive periodontits: a pilot study. *Eur J Oral Sci, 112*: 216-23, 2004.
46. Albandar JM. Epidemiology and risk factors of periodontal disease. *Dent Clin North Am, 49*: 517-32, 2005.
47. Tonetti MS, Mombelli A. Early-onset periodontitis. *Annals Periodontol, 4*:39-52, 1999.
48. Bimstein E. Extended kindred with 10 children with periodontitis: a seven-year follow-up report. *Pediatr Dent, 25*: 389-96, 2003.
49. Shaddox L, Wiedley J, Bimstein E, Magnuson M, Clare-Seltzer M, Aukhil I, Wallet SM. Hyper-Responsive Phenotype in Localized Aggressive Periodontitis. *J Dent Res, 89*: 143-8, 2010.
50. Shaddox LM, Wiedey J, Calderon NL, Magnusson I, Bimstein E, Bidwell JA, Zapert EF, Aukhil I, Wallet SM. Local inflammatory markers and systemic endotoxin in aggressive periodontitis. *J Dent Res, 90*: 1140-4, 2011.
51. Bimstein E, Matsson L, Soskolne AW, Lustmann J. Histologic characteristics of the gingiva associated with the primary and permanent teeth of children. *Pediatr Dent, 3*: 206-10, 1994
52. Suvan J, D'Aiuto F, Moles DR, Petrie A, Donos N. Association between overweight/obesity and periodontitis in adults. A systematic review. *Obes Rev, 12*:e381-404, 2011.
53. Meisel P, Wilke P, Biffar R, Holtfreter B, Wallascohofski H, Kocher T. Total tooth loss and systemic correlates of inflammation: role of obesity. *Obesity, 20*: 644-50, 2012.