2-1-2013

Principles of Periodontology

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Dentistry Faculty Research and Publications/School of Dentistry

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Abstract

Periodontal diseases are among the most common diseases affecting humans. Dental biofilm is a contributor to the etiology of most periodontal diseases. It is also widely accepted that immunological and inflammatory responses to biofilm components are manifested by signs and symptoms of periodontal disease. The outcome of such interaction is modulated by risk factors (modifiers), either inherent (genetic) or acquired (environmental), significantly affecting the initiation and progression of different periodontal disease phenotypes. While definitive genetic determinants responsible for either susceptibility or resistance to periodontal disease have yet to be identified, many factors affecting the pathogenesis have been described, including smoking, diabetes, obesity, medications, and nutrition. Currently, periodontal diseases are classified based upon clinical disease traits using radiographs and clinical examination. Advances in genomics, molecular biology, and personalized medicine may result in new guidelines for unambiguous disease definition and diagnosis in the future. Recent studies have implied relationships between periodontal diseases and systemic conditions. Answering critical questions regarding host-parasite interactions in periodontal diseases may provide new insight in the pathogenesis of other biomedical disorders. Therapeutic efforts have focused on the microbial nature of the infection, as active treatment centers on biofilm disruption by non-surgical mechanical debridement with antimicrobial and sometimes anti-inflammatory adjuncts. The surgical treatment aims at gaining access to periodontal lesions and correcting unfavorable gingival/osseous contours to achieve a periodontal architecture that will provide for more effective oral hygiene and periodontal maintenance. In addition, advances in tissue engineering have provided innovative means to regenerate/repair periodontal defects, based upon principles of guided tissue regeneration and utilization of growth factors/biologic mediators. To maintain periodontal stability, these treatments need to be supplemented with long-term maintenance (supportive periodontal therapy) programs.

Periodontology has been defined as 'the scientific study of the periodontium in health and disease' ([6]). The periodontium includes the gingiva, alveolar bone, periodontal ligament and root cementum, i.e. the tissues that support the teeth. The anatomy, histology and physiology of the normal periodontium have been described in great detail elsewhere.[347] They will not be covered in this context.

People exhibiting periodontal abnormalities, for example impairments of tissue integrity or function, are said to have periodontal diseases. These comprise a variety of phenotypes; defined by clinical signs and symptoms, they constitute the periodontal syndrome.[44, 397, 404] The most frequently observed phenotype is inflammation of the gingiva (gingivitis) induced by dental plaque (biofilm), and includes changes in tissue color, volume, temperature, crevicular exudate and bleeding upon gentle provocation with a probe.[251] The clinical signs of biofilm-associated gingivitis are reversible when adequate oral hygiene is implemented and maintained.[232] Less prevalent than gingivitis, but still observed in many persons, are the clinical signs of biofilm-associated periodontitis. They include periodontal pockets, attachment loss, bleeding upon probing, and radiographic bone loss.[117] Therapeutic efforts are directed towards elimination of the suspected underlying infection, typically leading to resolution of the signs of inflammation, tissue repair, and restoration of function and esthetics. The results of periodontal therapy may be stable over a long time period, but signs of disease may return unpredictably in terms of location, frequency and severity.

Many other phenotypes, frequently disease forms with severe signs and symptoms, have been described and classified.[145, 201] They are much less prevalent than typical biofilm-associated gingivitis or periodontitis. Some of the rare forms are related to systemic conditions; others are components of genetic syndromes. Diagnostic criteria frequently used to characterize the various phenotypes of periodontal syndrome are listed in Table 1.

Table 1. Diagnostic criteria used for periodontal diseases. A diagnosis can be made if two or more diagnostic signs are present. The initial diagnosis is further characterized using two or more modifiers

Diagnostic signs and symptoms
Gingival color (or texture, volume or contour)
Gingival necrosis
Gingival enlargement
Gingival recession
Bleeding on provocation
Bleeding on probing
Pockets
Attachment loss
Bone loss
Tooth mobility
Lateral migration
Pain
Modifiers
Age of onset (early or adult)
Progression (chronic or rapid)
Response to treatment (stable or recurrent)
Severity (mild, moderate or severe)
Extent (localized or generalized)

The objective of this overview of principles of periodontology is presentation of current and established concepts. Aspects of the history, classification, etiology, pathogenesis, epidemiology and treatment modalities of the most common periodontal diseases are discussed.

History

Early Observations

Periodontal diseases, unlike caries, are not a by-product of modern civilization. Manifesting themselves as *ante mortem* loss of alveolar bone, signs indicative of periodontal pathology were discovered in human specimens attributed to the Middle Pleistocene stage. For instance, indications of alveolar bone resorption were found in the 640- to 735,000-year-old Mauer mandible (*Homo heidelbergensis*) in Germany, and in a 169- to 191,000-year-old mandible that was unearthed at the Bau de l'Aubésier, Vaucluse, France.[91, 224] Such findings support the theory that periodontal diseases have plagued humans and their phylogenetic ancestors for a very long time.

Chinese physicians were probably first to describe signs of periodontal diseases. Diagnoses and treatments were presented in the earliest known textbook of Chinese medicine, Nei Ching, attributed to Huang Di (approximately 2700–2600 BC).[357] The ancient Egyptian Ebers Papyrus was written approximately 1000 years later (approximately 1550 BC). It is one of the oldest fully preserved medical documents, and contains several passages on remedies to cure conditions such as loose teeth and swollen gums ('flesh').[139] In Ancient India, Sushruta (approximately 6th century BC) illustrated a large number of surgical instruments, and explained 300 surgical procedures in the treatise Samhita. Sushruta taught a holistic approach to medical therapy. In pursuit of his philosophy, he described four periodontal conditions, offering probably the first classification of periodontal diseases.[357]

In 1563, the Italian Renaissance anatomist and physician Bartolomeo Eustachi (1514–1574) completed 'Libellus de Dentibus', the first book dedicated exclusively to the description of teeth.[127] He was the first to describe the periodontal ligament, as well as the deciduous and permanent dentitions. Eustachi's profound understanding of head anatomy and his amazing eye for the detail led him to link increased tooth mobility at an advanced age with widening of the space between the root and the alveolar bone. Similarly remarkable, he prescribed the removal of calculus and granulation tissue using scalers and curettes, respectively, to encourage re-attachment of periodontal tissues to loose teeth.[358]

From scurvy of the gum to Riggs' disease

Almost two centuries after Eustachi, the French surgeon-dentist Pierre Fauchard (1678–1761) published 'Le Chirurgien Dentiste', a two-volume book dedicated to the practice of dentistry. Fauchard's comprehensive work profoundly influenced the practice of dentistry. He pointed out that any dental disease can be allocated to one of only three classes, namely: (1) diseases with external cause, (2) (hidden) diseases that attack those tooth parts embedded in the periodontium, and (3) (symptomatic) diseases caused by the teeth.[113] Critical of the theories accepted by most physicians of his time, Fauchard postulated a humoral etiology of periodontal disease that is modulated by local factors, e.g. calculus. To prevent 'gum disease', he recommended cleaning the teeth, massaging the gingiva with an astringent liquid, and washing the mouth with wine and water. Because of the spongy appearance of the gingiva that had similarity to gingiva he observed in patients with scurvy, Fauchard called the phenotype 'scurvy of the gums'.

Fifty years later, the Scottish surgeon and scientist John Hunter (1728–1793) published 'A Practical Treatise on the Diseases of the Teeth intended as a supplement to the Natural History of those Parts', his second and less popular book on teeth and tooth-related structures. Hunter postulated that gradual loss of alveolar bone, associated pocket formation and gingival recession would inevitably result in tooth loss. He considered the process to be disease when it occurred early in life, but the result of natural aging in the elderly. Among gingival diseases, Hunter distinguished between cases that resembled Fauchard's 'scurvy of the gums' and cases of overgrown fibrotic tissue.[176]

Achievements in microbiology, a novel scientific discipline in the 19th century, changed the way periodontal diseases were viewed. Two German physicians, Robert Ficinus (1809–1852) and Adolph Witzel (1847–1906), deserve credit for associating bacteria with periodontal tooth loss.[63] In Europe, the term 'alveolar pyorrhea' was coined to describe any form of periodontal disorder unrelated to the aging process. According to Witzel, in patients exhibiting alveolar pyorrhea, the gingiva forms a pocket that allows bacteria to infect and destroy the underlying periosteum and ultimately alveolar bone. In the USA, John M. Riggs (1810–1885), also known as the father of periodontics, treated diseased pockets by painstakingly thorough calculus removal, curettage of soft tissues, and implementation of meticulous individual oral hygiene. He was convinced that all stages of periodontal disease, from the earliest signs of inflammation to tooth loss, were attributable to the same local etiology, i.e. calculus. Reportedly, Riggs' rigorous procedure healed more than 90% of his patients, a huge improvement over any previously known treatment. His success was soon recognized. In 1869, the Connecticut Valley Dental Association passed a resolution acknowledging Riggs as the first person ever to treat gum inflammation successfully.[264] Riggs' achievement also had a lasting effect on dental terminology; in the USA, the term 'scurvy of the gums' was replaced by 'Riggs disease'. Not for long, however. At the 1877 meeting of the American Dental Association, the Germany-born physician Frederick H. Rehwinkel (1825–1889) presented a paper on 'pyorrhea alveolaris', and ever since has been credited for introducing the European term to the American dental literature.[263] The term 'pyorrhea alveolaris' was quickly adopted by the dental community. It persisted deep into the 20th century, despite being rather a poor choice for the disease it purported to describe.

Focal infection theory

Willoughby D. Miller (1853–1907), whose work was very much influenced by Robert Koch, is best known for his groundbreaking ideas on the etiology of caries. He also postulated a role for bacteria in the etiology of alveolar pyorrhea,[270] and concluded that, in the presence of predisposing factors, many bacteria found normally in the mouth can cause periodontal disease (e.g., non-specific plaque hypothesis). Miller advocated that such bacteria could also play a role in the etiology of many other diseases in humans. He coined the expression 'focus of infection'.[271] but stopped short of promoting eradication of infected teeth to prevent or treat systemic illnesses. This step was made by Frank Billings (1854–1932), a highly respected American physician and academic leader. Billings and his student and colleague Edward C. Rosenow (1875–1966) promoted the theory of focal infection in the USA.[51, 331] Like Miller, Billings spent time in Europe, where the germ theory of disease, initiated by the groundbreaking discoveries of Koch, Lister, Pasteur and other luminaries, was heavily debated. According to Billings' theory, the germ carrier harbors pleiomorphic microorganisms that may cause disease at any time. Dissemination of such germs from a latent localized infection to a distant organ would occur through the blood and lymphatic systems. The focal infection paradigm was quickly adopted by many dentists and physicians, especially surgeons in the USA. Its clinical implementation, which was further promoted by substantial improvements in asepsis, led to uncountable unwarranted tooth extractions, tonsillectomies and other surgical procedures.[135] In 1928, Holman publicly questioned the validity of the focal infection theory.[164] Its importance started to decline in the 1930s as evidence accumulated indicating that surgical removal of suspected foci has no beneficial effect on the medical status of affected patients.[65, 326] It is tempting to speculate about apparent similarities between the focal infection theory and the so-called 'systemic link'. However, a closer look at the basis of the two paradigms reveals fundamental discrepancies, especially with regard to bacterial pleiomorphism and tissue lesion latency.

Periodontal disease classifications
Times of transition and consolidation

At the dawn of the 20th century, the realization that alveolar pyorrhea can be treated led to recognition of 'periodontia' as a dental specialty. The professional organization of periodontists now known as the American Academy of Periodontology was established in 1914 as the American Academy of Oral Prophylaxis and Periodontology. In Germany, the 'Arbeitsgemeinschaft für Paradentosen Forschung' was formed in 1924 with the goal of establishing an open communication platform for academicians and practitioners. However, the much needed information exchange was impeded by decidedly inconsistent terminology. Over subsequent decades, periodontists on both sides of the Atlantic met repeatedly to develop countless classification systems that reflected scientific progress as well as clinical utility. As a result of this effort, new nomenclatures were published at arbitrary intervals by professional bodies such as the American Academy of Periodontology, the American Dental Association, the Arbeitsgemeinschaft für Paradentosen Forschung and the World Dental Federation, among others. In addition, classifications were also contributed by individual authors.

One of the major biomedical accomplishments of the 20th century was the recognition that formal hypotheses can be tested in the clinic. Application of quantitative methods to clinical problem solving, albeit implemented slowly in most dental disciplines, had profound effects on the classification of periodontal diseases. The paucity of scientific evidence in support of periodontosis and occlusal trauma as classes of periodontal disease was initially acknowledged at the 1966 World Workshop in Periodontics,[1] and formalized 11 years later at the International Conference on Biology of Periodontal Disease. Only two classes of periodontal disease remained – juvenile periodontitis and chronic marginal periodontitis[417] – and these constituted the 1977 American Academy of Periodontology classification system.

In the meantime, the studies on experimental gingivitis by Harald Löe and his collaborators at the Royal Dental College in Aarhus, Denmark, ushered in the 'plaque era' of periodontology. Using novel index systems to assess plaque and gingivitis,[231, 360] they provided unequivocal experimental evidence for a direct relationship between the presence of dental bacterial plaque and gingivitis.[232, 233, 390] In addition, they demonstrated the full reversibility of all clinical signs of gingival pathology when oral hygiene was re-established. There is no question that the nature and results of these ground-breaking studies had a profound effect on most aspects of clinical periodontology.

Moreover, a destructive form of periodontal disease, most frequently observed around the central incisors and first molars in young people, initiated renewed interest in the disease class previously known as periodontosis. Baer[45] and Manson & Lehner[248] published initial clinical reports that were followed by studies of host defense mechanisms.[74, 77, 406] Because it was frequently diagnosed in adolescent patients, the form was re-named juvenile periodontitis.At the time of the 1977 International Conference on Biology of Periodontal Disease, the majority opinion among dentists was that, without treatment, gingivitis progresses to periodontitis, at a relatively constant rate, ultimately resulting in tooth loss. This view was challenged when Löe et al.[234] presented their results on the natural history of periodontal diseases. Performed in Sri Lanka in a population with no access to dental services and virtually no home care, the longitudinal study suggested the presence of three distinct sub-populations exhibiting clearly discernible patterns of disease progression: a cohort with no or minimal disease progression over time, a cohort with moderate disease progression, and a cohort with rapid disease progression. In most subjects, the presence of plaque and gingivitis did not lead to severe periodontitis or tooth loss. The centuries-old belief that linked alveolar bone and tooth loss to ageing was finally disproved.

These and other findings were reflected in a new classification that was first suggested at the 1986 World Workshop in Clinical Periodontics and modified at the World Workshop in Clinical Periodontics in 1989.[2] The revised system distinguished five classes of periodontal disease. In comparison to the 1986 taxonomy, a new class was introduced for periodontal diseases linked to systemic conditions. Moreover, criteria for disease onset and rate of progression were considered. One of the more obvious shortcomings of the 1989 classification was the absence of a category for gingival diseases. Also, many practicing periodontists felt that the emphasis of the classification on patient age at disease onset was not suitable for long-term patient care.

Finally, in 1993, the European Academy of Periodontology (now the European Federation of Periodontology) was founded at the 1st European Workshop on Periodontology. The European Academy of Periodontology adopted the American Academy of Periodontology's 1989 classification but suggested that an improved system should be considered based on three major classes: early-onset periodontitis, adult periodontitis and necrotizing periodontitis. Each of these was further defined by secondary descriptors (distribution within dentition, progression rate, treatment response, relation to systemic disease, microbiological characteristics, etc.).[32]

1999 International Workshop for Classification of Periodontal Diseases and Conditions

The currently used classification (2010) was implemented based on recommendations by the 1999 International Workshop for a Classification of Periodontal Diseases and Conditions (Table 2).[29] In addition to increasing the number of disease classes from five to eight, the revision included several substantial deviations from preceding classifications. Briefly, gingival diseases were included as an independent entity (class I). Chronic periodontitis (class II) and aggressive periodontitis (class III) replaced adult periodontitis and early-onset periodontitis, respectively, thus eliminating the classifier 'age'. The refractory class was abandoned, periodontitis as manifestation of systemic diseases (class IV) was modified and restricted to include only genetic and hematological diseases, and necrotizing periodontal diseases (class V) replaced necrotizing ulcerative periodontitis. Categories for abscesses of the periodontium (class VI), periodontitis associated with endodontic lesions (class VII) and developmental or acquired deformities and conditions (class VIII) completed the new classification system. Although not perfect, it reflects the current scientific understanding of the nature of periodontal

diseases, as well as the practice of periodontics. In the subsequent sections, the terminology of the 1999 classification will be used as appropriate.

Table 2. 1999 Classification of periodontal diseases and conditions

I: Gingival diseases
A Dental plaque-induced gingival diseases
B Non-plaque-induced gingival lesions
II: Chronic periodontitis
A Localized
B Generalized (>30% of sites are involved)
III: Aggressive periodontitis
A Localized
B Generalized (>30% of sites are involved)
IV: Periodontitis as a manifestation of systemic diseases
A Associated with hematological disorders
B Associated with genetic disorders
C Not otherwise specified
V: Necrotizing periodontal diseases
A Necrotizing ulcerative gingivitis
B Necrotizing ulcerative periodontitis
VI: Abscesses of the periodontium
A Gingival abscess
B Periodontal abscess
C Pericoronal abscess
VII: Periodontitis associated with endodontic lesions
A Combined periodontic–endodontic lesions
VIII: Developmental or acquired deformities and conditions
A Localized tooth-related factors that modify or predispose to plaque-induced gingival diseases/periodontitis
B Mucogingival deformities and conditions around teeth

| C Mucogingival deformities and conditions on edentulous ridges |
| D Occlusal trauma |

Classification limitations and next steps

Periodontal disease classification has evolved over a long time period. As such, it is the result of major paradigm shifts[30] that collectively have defined modern periodontology. Needless to say, all classifications have had their shortcomings, which exposed them to considerable criticism.[44, 175, 300, 323, 404] Armitage[30] probably put it best when he concluded that: 'Any attempt to group the entire constellation of periodontal diseases into an orderly and widely accepted classification system is fraught with difficulty, and inevitably considerable controversy. No matter how carefully the classification is developed, and how much thought and time are invested in the process, choices need to be made between equally unsatisfactory alternatives'.

The purpose of disease classification is to unambiguously link clinical phenotypes, defined by clinical observations and simple laboratory investigations, with diagnoses and ultimately disease-specific therapy (Table 3). The currently used system is a combination of broadly defined classification elements such as location, etiology and pathology. Some disease classes (II and III) are further refined using rule-based criteria, e.g. slight chronic periodontitis is defined by the inclusion criterion '1–2 mm of clinical attachment loss'. Other classes (I, IV and VIII) use relationship definitions rather than operational definitions for allocation of cases to sub-classes, e.g. periodontitis as a 'manifestation of' Down syndrome. Technically, allocation of a clinical phenotype to a disease class is achieved using information collected in a standard periodontal examination. Due to the inherent simplicity of the required clinical procedures, classification is an easy task for specialists in periodontics.

Table 3. Typical general characteristics of an ideal classification system

| • The classification corresponds to the nature of the disease being classified |
| • Every member of the universe of periodontal diseases ('periodontal syndrome') will fit in one and only one class/sub-class in the classification system |
| • The classification is useful |
| • The number of sub-classes is not excessive |
| • The set of classes can be constructed using a systematic procedure |

However, as mentioned above, the current classification has also received challenges. Of general concern is that some clinical phenotypes do not meet the classification criteria of any particular disease class. Examples have been described in the literature,[175, 300] and concern non-inflammatory destructive periodontal disease or atrophy. A weakness of many disease classifications is substantial overlap among classes. This occurs when the key properties of classes are too broadly defined. In such situations, clinical phenotypes cannot be allocated unequivocally, and mis-classification is possible. An example is the definition of aggressive periodontitis (class III) as 'rapid attachment loss and bone destruction'. Here the critical identifier refers to a subjective, temporal interpretation of a cross-sectional finding rather than objective information that can be obtained from patient examinations and records.

However, there is no universal agreement on threshold rates for rapid attachment loss and bone destruction. To mitigate the risk of mis-classification, selected biochemical (e.g. interleukin-1β and prostaglandin E_2) and microbiological (e.g. *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*) secondary identifiers have been proposed.[221] Another concern is the sensitivity and specificity of the methods used to collect patient information. Data on change in probing depth, clinical attachment and radiographic bone level are collected as the result of disease history. The methods used to generate such information lack the sensitivity required to detect the subtle sub-clinical changes that occur before tissue damage is clinically obvious. In addition, they are associated with substantial measurement error, which affects diagnostic specificity.

Our understanding of the fundamental mechanisms involved in onset and progression of most diseases, including those affecting the periodontium, remains incomplete. The already substantial amount of knowledge acquired from clinical and laboratory research regarding the etiology and pathomechanisms responsible for periodontal diseases has not yet paid off in terms of development of potent preventive and therapeutic measures for the *individual patient*. However, this situation will change. Progress achieved in the post-genomic disciplines of transcriptomics, proteomics, metabolomics and systems biology will permit a much more accurate and precise characterization and definition of disease at the phenotype level. In the not so distant future, such information could be used for identification of phenotypic differences among patients suffering from the same disease, subsequently leading to individualized, patient-specific therapies.[239]

Etiology

It is accepted that dental plaque microorganisms existing in the form of biofilms are primary etiological agents of periodontal diseases. Biofilms are matrix-enclosed bacterial communities that adhere to each other and to surfaces or interfaces. Enormous advances in biology and technology have provided ever more sophisticated tools for the investigation of dental biofilms. Introduction of the GasPak system[59] and the anaerobic glove box[27] allowed discovery of numerous fastidious anaerobic planktonic species in the oral cavity.[274, 365] Due to this advancement in anaerobiosis, coupled with epidemiological data, it was possible to associate a population shift toward certain gram-negative anaerobic species in dental plaque biofilms with the initiation and progression of periodontal diseases. However, it was the application of DNA-based assays, polymerase chain reaction and confocal microscopy[71, 206, 212, 217, 304, 366] that deepened our understanding of the formation, maturation and ecology of dental plaque biofilms.

The epithelia lining the mouth and the exposed tooth surfaces constitute the adherence substrate for oral biofilms (Fig. 1). Oral bacteria are initially acquired by contact with an infected family member at birth or at later life stages.[401] The conditions for bacteria to initiate successful colonization vary greatly depending on tissue type, location, and exposure to external shear forces. The gingival sulcus, and especially the col region, which forms the bridge between adjacent gingival papillae, offer protected niches that favor bacterial settling. Pioneer colonizers include oral species of the genera *Streptococcus*, *Veillonella*, *Prevotella*, *Neisseria*, *Gemella*, *Actinomyces* and others.[302] During biofilm maturation, bacteria interact with each other within and between species via surface-associated structures (co-aggregation), leading to a unique spatial organization.[229] As part of a sophisticated ecological system, biofilm residents communicate through exchange of genetic information and quorum sensing, a mechanism that allows coordination of their gene expression according to population density.[47, 379] In addition, biofilm bacteria facilitate processing and uptake of nutrients, and protect themselves from other species (by producing bacteriocins), the host and harsh environments,[245] allowing them to establish stable communities.[214]
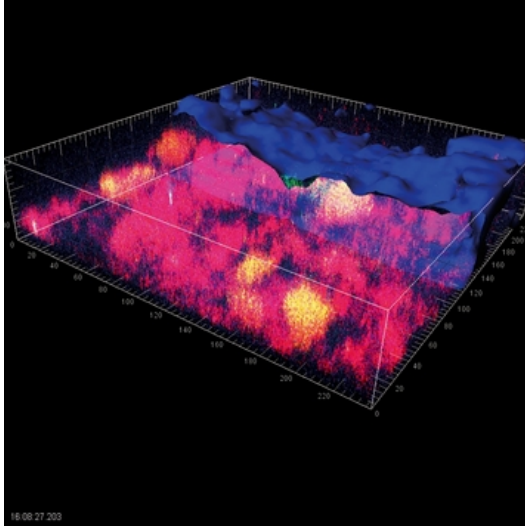
Figure 1. Properties of bacterial biofilms. Bacterial cells in a biofilm are held together by a matrix composed of extracellular polysaccharides, proteins, and other compounds. Biofilm development occurs in response to extracellular signals, both environmental and self-produced. Biofilms protect bacteria from a wide array of insults as diverse as antibiotics, predators, and the human immune system. The biofilm shown in the figure was grown for 3 days on a human enamel sliver worn by a healthy volunteer in the region of the maxillary premolars and molars. The surface to be imaged was facing towards the natural teeth to simulate retention areas. The biofilm was stained using fluorescent in situ hybridization (FISH) to show streptococci (yellow) and all bacteria (red). Reflected imaging (blue) was used to show the surface of the plaque and the slime matrix between the bacteria in the biofilm. The plaque biofilm was composed of dense clusters of streptococci interspersed with clusters formed by other bacteria. The scales on the x, y and z axes are in 1 μm increments. Biofilm image courtesy of Drs. Christiane von Ohle (Department of Conservative Dentistry, Tübingen, Germany) and Paul Stoodley (National Centre for Advanced Tribology Southampton, Southampton University, UK).

Mature dental biofilms can host a large variety of bacterial genera. Molecular detection of the microflora in the oral cavity has led to identification of approximately 700 bacterial species or phylotypes.[12, 212, 304] Approximately 50–60 species can be identified in a typical plaque sample when 16S rRNA probes are used.[329] 16S rRNA is a highly conserved gene sequence that permits estimation of evolutionary distance and relatedness of organisms.[78] Species compositions of dental biofilms vary greatly from sample to sample and are site-specific.[305] From initial colonization to formation of mature and potentially pathogenic supra- and subgingival communities, dental biofilms pass through several stages, including colonization, growth of commensal bacteria, and integration and invasion of pathogenic species.[207] Such opportunistic pathogens co-exist with other biofilm residents until changed environmental conditions favor their expansion and expression of their pathogenic properties. The bacterial composition of mature biofilms sampled in the gingival sulcus of periodontally healthy subjects over an extended time period shows a high level of temporal stability. In contrast, in subjects whose clinical status changes from health to disease or *vice versa*, many bacterial species disappear or emerge.[213, 368, 384] Likewise, periodontal diseases are considered to be opportunistic polymicrobial infections. Putative bacterial pathogens associated with periodontal diseases have been identified in subgingival biofilms. These include *A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Eikenella corrodens*, *Campylobacter rectus*, *Parvimonas micra* (previously *Peptostreptococcus micros*) and *Streptococcus intermedius.* Three species, *P. gingivalis*, *T. forsythia* and *T. denticola*, have been

designated as 'the red complex',[367] and are implicated in progression of chronic periodontitis. Numerous virulence factors, which can initiate and modulate pathways of the host response, were identified and characterized from these species.[165, 386] *P. gingivalis*(previously *Bacteroides gingivalis*), a gram-negative black-pigmented, immotile obligate anaerobe, is a late or secondary colonizer that depends on the presence of other biofilm species.[281] Its virulence potential is characterized by: (1) adhesion and co-aggregation mediated by fimbriae, vesicles, several hemagglutinins and outer membrane proteins, (2) evasion of host responses mediated by capsule lipopolysaccharides, and immunoglobulin and complement proteases, and (3) tissue damage mediated by a large number of peptidases that enable tissue invasion and destruction, and production of toxic metabolic end-products.[281] *T. forsythia* (previously *Bacteroides forsythus*) is a fastidious, non-motile, spindle-shaped, obligate anaerobic gram-negative rod whose growth in biofilms depends on co-aggregation with *P. gingivalis* or *F. nucleatum*. It secretes proteolytic enzymes and sialidase, and can induce apoptosis. Furthermore, *T. forsythia* can adhere to and invade epithelial cells and extracellular matrix components via the cell surface-associated BspA protein. The invasion is enhanced in the presence of *P. gingivalis*.[177] In addition, *T. forsythia* possesses a unique surface structure called a surface (S-) layer that is involved in hemagglutination and adherence/invasion of epithelial cells.[335] *T. denticola* is a gram-negative, aero-tolerant anaerobic spirochete. It is a late colonizer, and adheres readily to other bacteria, such as *P. gingivalis*, *T. forsythia* and *F. nucleatum*, using various adhesins. *T. denticola* also possesses numerous proteinases and peptidases. The functions of selected virulence factors identified from these periodontal pathogens have been validated by construction of isogenic mutants and animal studies.[166]

Aggregatibacter actinomycetemcomitans (previously *Actinobacillus actinomycetemcomitans*)[285] is a putative pathogen that has been associated with aggressive (previously known as 'juvenile') forms of periodontitis.[115, 363, 429] The oral cavity is its only known natural habitat. It is isolated regularly and in large numbers from various oral mucosal surfaces, even in toddlers and in the absence of periodontal pathology.[218, 385] Serotype b, one of five defined serotypes, can be isolated primarily from periodontal pockets in subjects with localized aggressive periodontitis.[428] In addition to its ability to colonize, *A. actinomycetemcomitans* can invade epithelial cells,[265] secrete a leukotoxin[42, 157] and induce apoptosis.[192] *A. actinomycetemcomitans* shows clonality in virulence, as leukotoxin production is greatly increased in clone JP2.[199] This clone belongs to serotype b and has a 530 bp deletion in the promoter region of the leukotoxin gene operon. This deletion is most likely responsible for the increased toxin production. Originally discovered in an 8-year-old Moroccan child with aggressive periodontitis,[149] the clone has also been isolated from Africans with a history of aggressive periodontitis in other parts of the world. The restriction of infection with JP2 to individuals of West- and North-African descent implies great colonization stability and a vertical transmission pathway from mother to child. Moreover, this allowed the investigators to track JP2's emergence on the African continent back in time for hundreds of years.[199] While infection with JP2 is a somewhat unique finding, it sheds light on the importance of specific bacteria in certain forms of periodontal disease, as well as the potential value of microbiological screening[309] for early detection in susceptible subjects.

Pathogenesis
The characteristic gingival and periodontal lesions are the result of biofilm-induced, orchestrated inflammatory responses involving the innate and adaptive arms of the immune system. Inflammation that remains limited to the gingiva is the outcome of a well-balanced symbiosis between biofilms and the host tissues, while periodontitis is the result of breakdown of this symbiosis. Moreover, it may be speculated that even the most common forms of periodontal diseases are merely analogous phenotypes of different pathogenetic pathways, initiated by biofilm products, of which only a few lead to tissue destruction in susceptible hosts. Much progress has been made at all levels of inquiry towards

understanding these pathways.[209, 295, 296, 298] Figure 2 shows a highly simplified model of the inflammatory pathway that can lead to tissue destruction, and it is explained below.
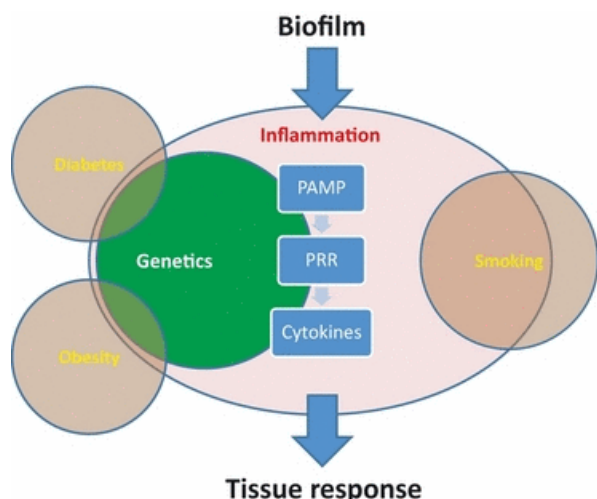

Figure 2. Inflammatory pathways are initiated by biofilm bacteria or products, and ultimately produce a tissue response, i.e. gingivitis or periodontitis. The type and strength of the response are determined by pathogen-associated molecular patterns (PAMPs) and the subject's genetic make-up, and modulated by the presence or absence of modifying factors, including diabetes, obesity, smoking, and others. For example, the PAMP lipopolysaccharide from gram-negative bacteria (e.g. Porphyromonas gingivalis or Tannerella forsythia), first binds via the CD14 receptor to Toll-like receptor 4, a pattern recognition receptor (PRR) that is expressed on polymorphonuclear leukocytes, as well as gingival and junctional epithelia. Activation of Toll-like receptor   4 also requires the presence of protein MD2, and engages a set of response proteins. Subsequently, intracellular signal cascades are turned on, resulting in a Toll-like receptor-specific reaction. Transition from the innate to the adaptive response is initiated by Toll-like receptor-triggered cytokine and chemokine production, and involves activation of antigen-presenting cells, as well as T-cell differentiation and regulation.

Basically, dental plaque biofilms are in constant interaction with their underlying substrates, i.e. the tooth surface, junctional epithelium, gingival epithelium and pocket epithelium. They receive nutrients from the saliva, crevicular fluid, cell debris and food. Considering biofilms a nuisance, without any benefit to the host, may be a big mistake. Not only do biofilms affect the host, there is mounting evidence that the host's responses similarly influence the metabolism and composition of biofilms. In a healthy person, host defense and biofilms co-exist in a mutually beneficial symbiotic state.[167, 253]

Bacteria are released continuously from dental biofilms, and to a large extent are eliminated before they elicit any host response. Significant bacterial invasion is not observed in subjects with clinically healthy periodontal tissues. Various physiological mechanisms are in place to maintain tissue integrity; bacterial products are rinsed off by the continuous saliva flow, crevicular fluid flushes the gingival sulcus, and the high turnover of the junctional and gingival epithelia eliminates bacteria-loaded superficial cells.[60, 348]

In addition to the mechanical cleansing action, highly potent first-line antimicrobial defense systems can sense and destroy intruders. Such systems include peptides found in the saliva (histatins, cathelicidins and others), epithelium, neutrophils,[93] and molecules described as pattern recognition receptors (PRRs).[73] α-defensins are observed in the junctional epithelium, where they are associated with polymorphonuclear leukocytes. These cells constantly migrate towards the gingival sulcus, responding

to a gradient of interleukin-8 that is expressed in the junctional and sulcus epithelium.[395] β-defensins are found in gingival and pocket epithelia, where they are constitutively expressed.[211] In addition to exhibiting excellent antibacterial properties, defensins can activate the complement cascade, up-regulate production of the chemokine interleukin-8 in epithelial cells, and attract immune cells.[254] PRRs are typically found on the surface of polymorphonuclear leukocytes, macrophages, dendritic cells, endothelial cells, mucosal epithelium cells and lymphocytes.[189] They include two functional families. Endocytic PRRs are located on the surface of phagocytes. They facilitate the attachment of microorganisms, leading to their engulfment and destruction. Signaling PRRs are located on the surface of a greater variety of cells. They recognize structurally highly conserved pathogen-associated molecular patterns (PAMPs) on microorganisms. PAMPs include lipopolysaccharide, teichoic acids, sugar residues, *N*-formyl peptides and others. Binding of PAMPs to PRRs promotes the synthesis and secretion of intracellular regulatory molecules such as cytokines that are crucial for initiating innate immunity and adaptive immunity.

Recently, Toll-like receptors, a subgroup of the signaling family of PRRs, were identified in periodontal tissues.[246] Interaction between a PRR and its PAMP leads to a rapid cascade of events, including formation of a PRR–ligand complex that can be internalized, activation of Toll-like receptors and NFκB, and transcriptional activation resulting in the synthesis of reactive oxygen species, reactive nitrogen species, cytokines (interleukin-1, interleukin-12 and tumor necrosis factor-α), and chemokines (interleukin-8, monocyte chemoattractant protein-1, regulated on activation, normal T cell expressed and secreted (RANTES)). These compounds trigger an immediate inflammatory response, and enable migration of additional leukocytes from the blood to the site of inflammation. CD14 is another PRR that is expressed on polymorphonuclear leukocytes, macrophages and monocytes. It enhances the ability of Toll-like receptor   4 to respond to lipopolysaccharide. The complex formed of CD14, lipopolysaccharide and Toll-like receptor   4 increases the production of cytokines and chemokines, leading to inflammation and activation of the complement cascade and the coagulation pathway. Finally, Toll-like receptors instruct dendritic cells to initiate a highly differentiated, specific T-cell response.[14] Thus, defensins and PRRs not only neutralize microbial components, they also constitute an important link between innate and adaptive immune responses.

Increased vascular leakage and activation of serum protein systems potentiate the local acute inflammatory response. Gingival crevicular fluid flows at an increased rate.[108, 134] During early phases of lesion development, a dense polymorphonuclear leukocyte-dominated infiltrate is found in the biofilm-adjacent gingival compartment. To destroy potential intruders, polymorphonuclear leukocytes release proteases, prostaglandins and other inflammation-enhancing molecules, as well as highly potent reactive oxygen and nitrogen species. These effectors do not discriminate between host and bacteria, resulting in collateral damage to gingival connective tissue. A successful inflammatory response eliminates the infectious agent and initiates tissue repair. However, if the infection prevails, as a result of persisting inflammation and instructed by macrophages and dendritic cells, cells of the adaptive immune system appear, and the lesion takes on chronic traits. T-cells and B-cells start to accumulate, and ultimately dominate the lesion. Their proportions are determined by the type of immune response elicited by the antigens and the presence of modulating cytokines. Plasma cells develop from B   cells and produce antibodies in response to bacterial antigens and mitogens. In a typical gingival lesion, T cells predominate. T-helper cell subsets (Th1 or Th2) develop from T cells depending on the types and amount of cytokines released. The balance between T-helper cell subsets is critical for the immunoregulation of periodontal disease.[356] Th1 cells predominate in stable periodontal lesions, but a strong presence of Th2 cells indicates a shift towards lesion progression, with a predominance of plasma cells.[355]

The local physiological defense mechanisms are very robust and exhibit substantial redundancy. In fact, many people show minimal or no periodontal destruction despite experiencing gingivitis as a result of lifelong poor oral hygiene.[234] However, robust systems are weak when their non-redundant components are attacked,[204] resulting in deficiencies in the immune system. Such attacks may have critical consequences for periodontal tissue integrity, as illustrated in patients with (genetic or acquired) immune deficiencies. In particular, class IV.B cases of periodontal disease have been associated with mutations in the genes encoding for polymorphonuclear leukocyte elastase (severe congenital neutropenia), Chediak–Higashi syndrome 1 protein (Chediak–Higashi syndrome), integrin-β2 (leukocyte adhesion deficiency), cathepsin C (Papillon–Lefèvre syndrome) and others.[145]

Resorption of the alveolar bone is a defining characteristic of many periodontal diseases. Several inflammatory pathways can result in bone destruction.[387] Macrophages, in addition to processing and presenting antigens for activation of the specific immune response, also produce cytokines and enzymes that induce bone resorption. Recently, an alternative mechanism was described that involves three members of the tumor necrosis factor receptor family: the receptor activator of NFκB (RANK), the receptor activator of NFκB ligand (RANKL) and osteoprotegerin.[193, 230] The ligand RANKL is found on osteoblasts, but is also expressed by lymphocytes present in the inflammatory infiltrate. RANK is expressed on mature osteoclasts and their precursors, and osteoprotegerin is synthesized by mesenchymal cells. The interaction of RANK and RANKL initiates the differentiation and activation of bone-resorbing osteoclasts, and can be blocked by the decoy ligand osteoprotegerin. RANKL and osteoprotegerin are found in crevicular fluid, and their relative levels appear to predict disease.[54]

Epidemiology

General trends

Gingival and periodontal diseases occur globally and among virtually all populations that have been studied to date.[19] Clinical signs of periodontal destruction may be absent in individuals of any age, but there is little evidence supporting the existence of periodontitis-resistant populations. However, two defined apparently resistant cohorts with no access to dental care were described in Namaqualand and Crossroads (South Africa).[13, 324] They showed minimal clinical periodontal breakdown at any age, despite the presence of a heavy plaque load and gingivitis.

The World Health Organization performed extensive surveys of the periodontal status of potentially under-served populations around the globe, especially in developing countries.[307] Using the Community Periodontal Index for Treatment Needs to assess prevalence, a majority of subjects examined had gingivitis and 10–15% of adults had periodontal pockets ≥6 mm deep. In contrast to common belief, periodontal diseases are not the most important factor for tooth loss in many Asian and most African populations. In fact, surveys have indicated that, in Africa, most people retain the majority of their teeth throught their lives.[43, 83]

In the USA, based on estimates obtained from the National Health and Nutrition Examinations Surveys performed from 1988 to 1994 (NHANES III),[278] the overall prevalence of moderate to severe signs of periodontitis among adults was 7.3%, corresponding to one affected adult person in 14.[19, 53] Approximately one in five adults had slight periodontitis, one in ten had moderate periodontitis, and one in 30 showed signs of severe periodontitis. The prevalence of periodontitis increased with population age, but the prevalence of more severe forms peaked at 70 years and leveled off thereafter.[19] Periodontitis was more frequently diagnosed in men than in women. Substantial racial and ethnical disparities were observed. Adult black people were almost twice as likely to exhibit periodontitis as white adults, suggesting a significant racial gap.[53]

In the analysis of the more recent NHANES 1999–2000 data,[53] the overall prevalence of moderate to severe periodontitis was only 4.2% (compared to 7.3%), suggesting a potentially substantial reduction in disease burden over the past decade. Surveys performed in Europe have corroborated the suspected 'secular trend' of prevalence reduction in periodontal diseases among adults.[334, 362] A comparison over a 30-year period of the prevalence of various clinical signs of periodontal disease in Swedish subjects aged 20–70 years revealed remarkable changes (Fig. 3).[169] Over the surveyed period, the proportion of periodontally healthy individuals improved from 8% to 44%. The increment compensated for the decrease in the proportion of individuals with gingivitis or moderate alveolar bone loss. In contrast, the proportion of subjects exhibiting signs of severe periodontal disease was small and did not change over time. Improvements in oral hygiene, changes in lifestyle and adoption of less risky behavior, in particular recognition of deleterious smoking effects, have been proposed to explain the unexpected decline. However, much more work is undoubtedly required to confirm and understand this highly desirable trend.
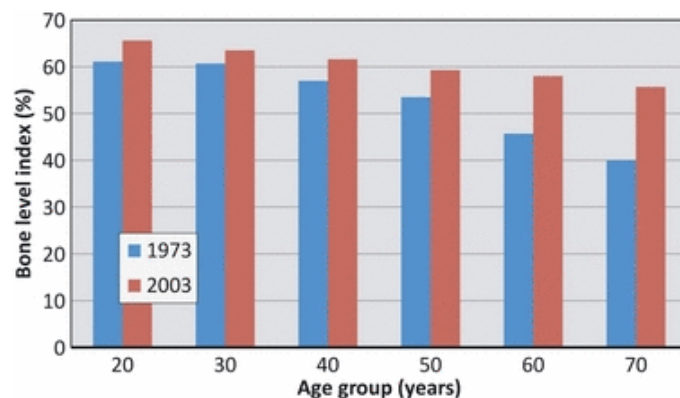

Figure 3. An improvement in alveolar bone index was observed over a 30-year time period in Scandinavians, as indicated by the blue (1973) and red (2003) bars. Mean alveolar bone indices were estimated from radiographs obtained in cross-sectional studies performed in 1973 and 2003. Age groups from 20 to 70 years are shown. Data from.[169]

Aggressive forms of periodontitis

Aggressive forms of periodontitis are defined by rapid localized or generalized loss of the supportive periodontal structures, and occur in family clusters in otherwise medically healthy subjects.[221] Aggressive forms can affect the primary or permanent dentition. Typically, susceptible patients are less than 30 years old at disease onset.[16] The similar phenotypes of aggressive periodontal disease are probably the clinical expression of multiple disease forms with discrete etiologies.

The reported prevalence of early-onset aggressive periodontitis varies from study to study. The comparability of the data is affected by the somewhat ambiguous disease definitions and the various diagnostic techniques used. A review concluded that aggressive forms of periodontitis have a low prevalence in most regions of the world, occurring in 0.1–1.0% of the population.[20] For reasons that are unclear at present, this disease form is seen substantially more frequently among young black subjects. A prevalence of 2.6% was reported in a sample representative of high school students in the USA.[15]

Even higher disease prevalences of 6.5% and 7.6% were observed in two cohorts of adolescents and young adults in Uganda[18] and Morocco,[149] respectively. These subjects were carriers of *A. actinomycetemcomitans* clone JP2, which is endemic in Morocco. Carriers of the JP2 clone, who

were free of clinical disease signs at the first examination, had a relative risk of 18.0 (95% CI 7.8–41.2) of experiencing periodontal attachment loss during the 5-year observation period.[150]

Although earlier reports by Saxén[338] showed a female majority among subjects with early-onset aggressive periodontitis, a more recent national survey conducted in the USA did not corroborate this observation.[235] Furthermore, based on the results of a genetic segregation analysis performed in 100 families in the USA, the aggressive disease trait has an autosomal dominant inheritance pattern.[249] This contrasts with the autosomal recessive inheritance pattern identified in northern Europe,[339] suggesting a different pathway to disease for each of the two populations.

Necrotizing periodontal diseases

Necrotizing periodontal diseases feature ulceration and necrosis of the interdental papillae, spontaneous bleeding, pain and a removable pseudomembrane.[4] Advanced cases involve alveolar bone resorption, may be generalized, and may lead to fever, malaise and lymphadenopathy.[276] Necrotizing periodontal diseases are observed frequently in parts of Africa, Asia and Latin America, mainly in socially disadvantaged children. For example, in an urban South African clinic population, the prevalence of acute necrotizing ulcerative gingivitis was 3%. Males were more frequently affected than females. Seventy-three per cent of the patients were children between 5 and 12 years old. The seasonal occurrence varied greatly, with most cases diagnosed in the summer (relative risk 6.57; 95% CI 4.96–8.70).[28] In contrast, necrotizing periodontal disease is now rarely observed in the general population of Europe and North America, as confirmed in a recent study among 18- to 22-year-old military recruits in Switzerland.[82]

A high prevalence of necrotizing periodontal disease has been observed in HIV-infected subjects.[223, 306, 314] Based on this finding, the presence of necrotizing periodontal disease has been recommended for use as a surrogate marker of HIV-associated immune deficiency and AIDS.[125]

Risk modifiers

Development and progression of periodontal disease in an individual are 'personalized' by a number of endogenous and exogenous factors (Table 4). Assessment, knowledge and proper management of these factors facilitate the prevention of disease or its containment in the case of an existing periodontal condition. An intelligent algorithm that estimates the risk for periodontal disease based on easily accessible clinical information was developed, validated and implemented in practice.[299, 301]

Table 4.   A selection of risk modifiers of chronic and aggressive periodontitis

Risk modifier
Age of patient
Bleeding on probing
Diabetes mellitus
Furcation involvement
History of periodontal surgery
Probing (pocket) depth

Radiographic bone level
Restoration below the gingival margin
Root calculus
Single-nucleotide polymorphisms
Smoking history
Vertical bone lesions

Smoking

An association between smoking and alveolar bone loss was first reported by Waerhaug's group in the late 1950s.[31] Cigarette smoking was identified to be an age-independent risk indicator for periodontal disease in the Tecumseh Community Health Study in Michigan.[378] This greatly increased risk of smokers experiencing periodontal breakdown was confirmed in many studies.[36, 104, 163, 255, 315] An analysis of the NHANES   III survey data concluded that smokers have a four times greater risk of periodontitis than non-smokers.[17] The data suggest a dose–effect relationship between the number of cigarettes smoked per day and the likelihood of developing periodontitis. The research further estimated that more than 40% of cases of periodontitis among adults can be attributed to current cigarette smoking. Of major clinical relevance is the observation that smoking impairs wound healing following scaling and root planning,[137, 182, 403] periodontal surgery[24, 111, 376, 396] and guided tissue regeneration procedures.[240] Mechanisms for smoking-induced adverse effects have been postulated, but the precise molecular pathways remain to be identified.[46, 49] Smoking is unquestionably a major risk modifier for most inflammatory periodontal diseases.

Genetics

It has been well established from twin studies that genetic factors contribute substantially to the risk of chronic periodontitis.[84, 266, 267] A population-based study[275] in more than 10,000 Swedish twin pairs estimated that genetics-attributable contributions to the cummulative risk of periodontal disease amounted to 39% (95% CI 31–47%) and 33% (95% CI 24–42%) in women and men, respectively. Furthermore, the magnitude of the effect was strongly influenced by age and smoking status, suggesting substantial gene–environment interaction.

Based on the currently available evidence, chronic and aggressive forms of periodontitis are not associated with single gene mutations or acquired molecular abnormalities. However, DNA sequence variations in genes that result from alteration of a single nucleotide can substantially affect the disease phenotype. Single-nucleotide polymorphisms are thought to play a role in periodontal diseases.[10] The commercial availability of high-throughput, low-cost technology has boosted research in genome-based risk factors for complex diseases. As a result, the association of numerous polymorphisms with specific forms of periodontal disease was investigated.[58, 114, 120, 130, 181, 208, 380, 383, 422, 423] Examples of single-nucleotide polymorphisms that were considered in such studies include those in interleukin-1, interleukin-6, interleukin-10, interleukin-12RB2, Fc-γ, matrix metalloproteinase-9 and tumor necrosis factor-α, to name but a few. In addition to obtaining a better understanding of the disease process, such polymorphisms may be used as diagnostic or prognostic markers. The PST™ genetic test (Interleukin Genetics Inc., Waltham, MA, USA) has been offered to patients with periodontitis. It tests for single-nucleotide polymorphisms of interleukin-1 genes, and has shown moderate sensitivity and specificity in

predicting disease progression in non-smokers. The test's cost-effectiveness was investigated using a mathematical model.[160] The authors' conclusion that more benefits would result if risk-specific treatments were available is very much to the point.

Epigenetic alterations to the genome may also play a significant role in disease expression. These changes involve both methylation of DNA and post-translational modification of histone proteins. The epigenetic profile is modified by the environment over time, and may have substantial implications for periodontal disease expression.[421]

Diabetes

Estimates suggest that approximately 7% of the total population in the USA have diabetes, and the prevalence is increasing.[66] Subjects with a history of type 2 diabetes mellitus have a higher prevalence and severity of periodontitis, as shown in Pima Indians.[110] In another study, 25- to 74-year-old diabetics had significantly increased likelihood of experiencing attachment loss.[136] Recently, an increased prevalence of periodontitis was shown in children and teenagers with type 1 diabetes compared to age-matched controls.[217] Subjects with poor glycemic control showed faster recurrence of periodontal pockets after periodontal treatment than non-diabetic controls.[389] Westfelt et al.[416] compared the outcomes of periodontal surgical treatment in subjects with well-controlled type 1 and 2 diabetes with those in sex- and age-matched controls over a 5-year period. All subjects had moderate to advanced forms of chronic periodontitis. The results showed no difference between the two treatment groups, suggesting that well-controlled diabetics can maintain healthy periodontal conditions. There has been increased interest in the question of whether or not treatment of periodontal diseases leads to improved glycemic control in diabetic patients.[178] Nine controlled clinical trials were performed in an attempt to answer this important question, and the results were summarized meta-analytically.[94] The overall results indicated that periodontal treatment led to a statistically significant reduction in the surrogate marker glycosylated hemoglobin (HbA1c). However, the authors' enthusiasm about this favorable finding was guarded because of the small size of the reduction (<1%) and its lack of robustness. They therefore concluded that there is still insufficient evidence for global recommendation of periodontal treatment as an effective measure to reduce glycosylated hemoglobin (HbA1c) in adult subjects.

Obesity

Obesity is a major risk contributor to disease and death worldwide. More than 60% of adults in the USA are overweight, and approximately 30% are obese.[151] Close relationships have been established between obesity and diabetes, hypertension, coronary heart disease and stroke, and cancer.[146] Body fat, which is accumulated to excess in obese people, is produced by adipocytes. In addition to producing fat, these cells also release molecules that affect insulin resistance, and secrete hormones and cytokines, leading to a hyperinflammatory state. In a brief editorial note, Saito et al.[336] described their observation that apparently healthy Japanese subjects with a BMI > 25 kg/m^2 had a significantly higher relative risk of periodontitis than subjects with a BMI < 20 kg/m^2. The association between obesity and periodontitis was subsequently substantiated by more extensive studies in various populations.[227, 310, 424]

Pregnancy

The female body is subject to substantial hormonal fluctuations, especially during pregnancy. The most remarkable hormonal change during pregnancy is the increasing production of estrogens and progesterone, which levels off approximately one month before delivery. By that time, estrogen blood levels have risen more than 100-fold. In addition, the type of estrogen secreted changes from estradiol to the less potent estriol. These hormones are mostly produced by the placenta, and the levels revert to pre-pregnancy levels within a few days after delivery. An increased prevalence and severity of gingival

inflammation were reported in pregnant women.[231, 247, 375] These changes appear to be independent of changes in plaque amount[168] and are reversible.[140] About one pregnant woman in 20 develops a highly vascular, edematous lesion known as pyogenic granuloma. The lesion occurs typically during the first two trimesters, and has a strong tendency to recur if excised during pregnancy. Although hormones are likely to play a significant role in the development of pyogenic granuloma, its etiology remains largely unknown.[216]

Medications

Early studies on the effect of oral contraceptives on parameters of periodontal health reported an increased prevalence and severity of gingivitis in subjects who were taking contraceptives than in controls.[250] The contraceptives used by study participants contained high doses of estrogen, progestin, or both. In contrast, the most frequently used products at the present time are low-dose combination preparations of estrogen (≤50 μg) and progestin (≤1 mg). A more recent study[382] used information collected in NHANES I and III to investigate the relationship between oral contraception use and periodontal parameters. The thorough analysis rejected the previously held notion that women on oral contraception are at higher risk of experiencing clinical signs of gingivitis or periodontitis.

Certain anticonvulsants (e.g. phenytoin), immunosuppressants (cyclosporine) and calcium channel blockers (e.g. nifedipine) have been associated with gingival enlargement.[7] The prevalence of this side-effect varies from 5% to 50% in adults.[79] For cyclosporine, the highest prevalence of gingival overgrowth was observed in children[191] and decreased with increasing patient age.[152] The severity ranged from small single lesions to massive growths that impaired function and esthetics.[147] The pathogenesis of drug-influenced gingival enlargement remains unresolved, although a multitude of contributing factors appear to be involved, including integrins, cytokines and matrix metalloproteinases. An interesting hypothesis proposed involvement of single-nucleotide polymorphisms of the *MDR1* gene, which encodes the drug-efflux pump P-glycoprotein. This effect was observed in a clinical study[98] that found severe cyclosporine-induced overgrowth in patients carrying the *MDR1* C3435T mutation.

Nutrition

For many centuries, a deficient diet was considered a cardinal factor in the development of periodontal diseases. The hypothesis was based on anecdotal evidence, and held up to its premise until animal experiments permitted its scientific test. Glickman[126] was among the first to investigate the effect of vitamin C on the periodontium in guinea pigs. His experiments confirmed that diets lacking certain vitamins or minerals can affect the development of periodontal tissues and bone. Specifically, the author concluded that a diet deficient in vitamin C resulted in generalized alveolar changes but was not responsible for periodontal pocket formation. Recently, Nishida et al.[284] reassessed the relationship between dietary vitamin C intake and periodontal disease using the powerful NHANES III database. They found that persons with low vitamin C intake (<30 mg/day) had a slightly increased likelihood of developing periodontitis when compared to a reference group with elevated intake (>180 mg/day).

Diets rich in whole grain have been associated with lower risk of diabetes and cardiovascular disease.[226] This desirable effect is probably the result of improved insulin sensitivity and improved glycemic control.[180] Merchant et al.[262] used information gathered in the Health Professionals Follow-up Study (HPFS) to investigate the relationship between intake of whole grain, refined grain or cereal fiber and risk of periodontitis. After 14 years of follow-up, men who consumed 3.4 servings per day (median) of whole grains were 23% less likely to be diagnosed with periodontal disease than those who consumed 0.3 servings per day (median). These intriguing results were further confirmed in a study using data from NHANES III that found an inverse association between serum total antioxidant capacity and periodontitis.[69, 70]

Systemic effects of periodontal disease

After several decades of relative absence from the scientific literature, new reports linking indicators of dental health with an increased risk for a variety of systemic diseases emerged in the 1980s and 1990s. Examples include associations with myocardial infarction,[257, 361] stroke,[236, 381] cardiovascular disease,[102] peripheral vascular disease,[261] adverse pregnancy outcomes[95, 289] and pneumonia.[118, 340, 341] The possibility that periodontal and other diseases of the human body could be linked created broad-based excitement among the dental community and beyond, and ushered in the era of periodontal medicine.[418] As a result, in a worldwide effort, hundreds of clinical and laboratory studies have been performed, leading to a much deeper understanding of periodontal diseases as part of overall health.

The foundation for an etiological role of periodontal diseases in general health is based on two assumptions. First, bacteria released from biofilms located in periodontal pockets can enter the bloodstream through ulcerations of the pocket epithelium and colonize other body parts, especially in patients with compromised immunity.[200, 342] Second, periodontal pathogens elicit inflammatory reactions in the affected tissues, stimulating the release of pro-inflammatory cytokines or acute-phase proteins, and contributing to systemic inflammation, possibly atherogenesis, and other pathology.[96, 200, 303]

Although many published (frequently small-scale) studies have reported statistical associations between parameters of oral health and systemic disease, the all-important cause/effect relationship awaits confirmation in large-scale longitudinal epidemiological and interventional studies. Examinations of the link between periodontitis and coronary heart disease using information collected in NHANES I did not show the expected strong association.[171, 172] Furthermore, a review of nine cohort studies found no or only weak associations after controlling for smoking or lifestyle factors.[174] The concern that confounding could mask the study outcome received additional support in the 6-month pilot trial of the National Institutes of Health-sponsored Periodontitis and Vascular Events (PAVE) study.[293] The trial showed that a beneficial effect of periodontal treatment on the surrogate marker hs-C-reactive protein was achieved only in non-obese subjects with cardiovascular disease, whereas it was not observed in obese subjects. Another National Institutes of Health-funded multi-centered study, the randomized controlled Obstetrics and Periodontal Therapy (OPT) trial, investigated the effect of non-surgical periodontal treatment on pre-term birth rates in more than 800 pregnant women exhibiting clinical signs of chronic periodontitis.[268] The investigation confirmed the safety and effectiveness of standard periodontal treatment in pregnant women, but did not detect significant treatment-induced reductions in the rate of pre-term birth or other birth-related outcomes.

It is too soon to draw a final conclusion as to whether the so-called 'systemic link' is of major public health relevance, or not. Caution is warranted. The biological plausibility model of the systemic link assumes that the larger the wound surface area, the greater the chances of bacteremia, and that the large wound surface persists over substantial time periods. Are some of the model assumptions overly optimistic? For example, the combined contact surface area between biofilms and pocket epithelium in patients with generalized periodontitis was estimated as up to 70 cm^2,[297] potentially resulting in an impressively large wound surface.[290] However, the overwhelming majority of patients with chronic periodontitis do not show signs of disease activity in all pockets simultaneously,[364] and phases of such activity are typically short-term. Indeed, detection of active periodontal disease is a daunting task in most patients because of its elusive character. The disease is often present at only a few sites, which could mean that the effective wound size is considerably smaller than previously estimated, possibly just a few square centimeters.[173, 282] Although not impossible, detection of remote effects of such a small wound is a formidable challenge.

Treatment modalities for gingivitis and periodontitis

Historical overview

Local mechanical debridement of the teeth and root surfaces has been advocated for centuries as a treatment for diseases of the periodontium, with descriptions of calculus removal being found in the ancient writings of almost all known civilizations. Various other therapies such as cauterization using thermal or chemical agents, use of astringents on the soft and hard tissues, as well as soft-tissue removal using curettes or surgical blades have been advocated at various times and in various cultures as treatments for periodontal diseases.[127, 128] Scientific and technical progress in the 19th and 20th centuries, including better understanding of the histopathology of the disease and its microbial etiology, as well as the development of radiography, local anesthesia and analgesia, made diagnosis and treatment of periodontal diseases more standardized although not truly cause-related.

After the seminal work by Löe et al.,[232] demonstrating the cause and effect relationship between bacterial plaque/biofilms and gingival inflammation, the second half of the 20th century saw an explosion of research on cause-related therapy for gingivitis and the most common phenotypes of periodontitis. These centered on mechanical and chemical methods to attack the microbial origins of disease. Later observations of differential host susceptibility to disease[162, 234] and the discovery of molecular mechanisms of tissue destruction in the periodontium[243] suggested anti-inflammatory or host modulation approaches as potential means to address periodontal syndromes.[202] Today it is universally agreed that effective periodontal therapy for plaque-related disease requires elimination of inflammation through re-establishment of a biologically acceptable 'clean' root surface. Current therapeutic approaches all aim to achieve that end with minimal removal of cementum. Antimicrobials and host-modulating agents may be used as adjuncts to this basic and arguably ancient mechanical approach to therapy. How, when and why these approaches fit into therapy is discussed below in the context of treatment sequence, with emphasis on the most common form of disease: chronic periodontitis.

Systemic and acute phases of treatment

General guidelines for dental treatment planning have been published[377] based on five treatment phases: systemic, acute, cause-related, surgical corrective and maintenance (Table 5). The systemic treatment phase is concerned with prevention of treatment complications, particularly in subjects in whom periodontitis is associated with systemic disease, as well as with protection against disease transmission. Another goal of the systemic phase is to optimize treatment outcomes by addressing important subject-based risk factors, such as smoking[163, 315] and diabetes.[389, 416] Although the systemic treatment phase is crucial in many periodontal disease phenotypes, the acute treatment phase is usually only implemented for symptomatic forms of periodontal disease, such as necrotizing periodontal diseases, abscesses of the periodontium, and sometimes in cases of periodontitis associated with endodontic lesions. In acute situations, the systemic treatment phase may be abbreviated, but cannot be ignored. For such situations, control of pain and infection is paramount. Basic treatment approaches for some common acute periodontal conditions are outlined in Fig. 4. As the majority of gingivitis and tissue-destructive periodontal diseases are non-painful, most of the treatment for these conditions occurs in the context of overall restoration of oral health during the active treatment phases.

Table 5. Guidelines for sequencing the treatment for periodontal patients. Modified and reproduced with permission from[377]

I: Systemic phase

A Consultation with patient's physician
B Pre-medication
C Stress/fear management
D Any necessary treatment considerations for systemic disease

II: Acute phase

A Emergency treatment for pain and infection
B Addressing the urgent chief complaint

III: Cause-related phase

A Oral hygiene education, patient motivation and risk assessment
B Mutual goal-setting for acceptable outcomes/endpoints of therapy
i: Implementation of strategies for risk reduction
C Excavation of deep carious lesions
i: Determine restorability
D Extraction of hopeless teeth along with non-surgical periodontal debridement
E Removal of plaque retentive factors
F Necessary endodontic and occlusal therapy
G Post-treatment re-evaluation
i: Objective assessment of endpoints of therapy

IV: Surgical corrective phase

A Resective/regenerative and implant surgical procedures
B Post-surgical re-evaluation
i: Objective assessment of endpoints of therapy
C Definitive prosthodontic restoration

V: Maintenance phase

A Periodic professional supportive care
B Reinforcement of oral hygiene instruction and motivation
C Annual multi-pronged periodontal stability and risk re-assessment
D Comprehensive professional supra- and subgingival plaque removal

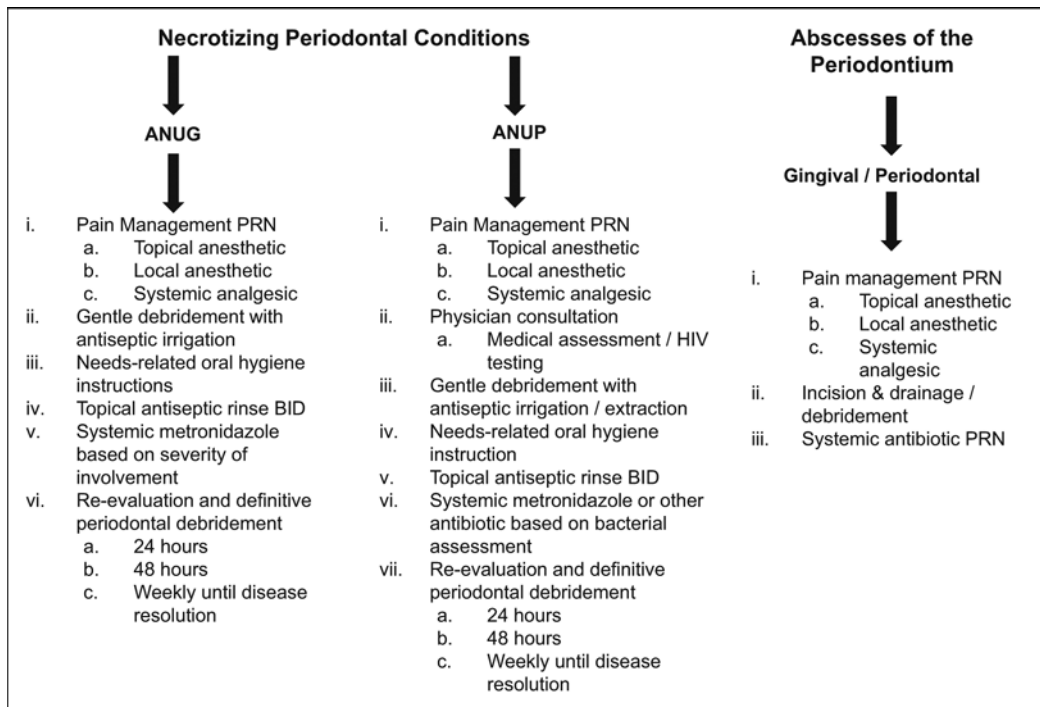| |
|---|
| E Radiographic updates and therapeutic interventions (as needed) |

Figure 4. Common treatment strategies for acute periodontal conditions. ANUG: acute, necrotizing, ulcerative gingivitis. ANUP: acute, necrotizing, ulcerative periodontitis. PRN: as needed. BID: twice a day.

Active treatment and maintenance

Periodontal treatment is often divided into disease control, surgical and maintenance phases. While variations in the therapeutic approach are necessary for different forms of periodontal disease, these three phases are generally applicable to asymptomatic periodontitis patients. The disease control phase has also been termed the 'initial' or 'cause-related' phase of treatment because it is primarily focused on elimination of pathogenic subgingival biofilms as well as removal of factors that promote biofilm formation and subsequent destructive inflammation. An overview of common treatment strategies for gingivitis is presented in Fig. 5. For plaque-induced gingivitis, the treatment centers on professional and personal plaque removal, with proper training in needs-related oral hygiene measures being critical. Antiseptics can also play a role in reducing plaque and gingivitis. For non-plaque-induced gingivitis, it is important to identify the source of inflammation and reduce or eliminate it whenever possible. Common treatment approaches for chronic and aggressive periodontitis, in which tissue destruction has occurred, are outlined in Fig. 6. In each case, active treatment centers on disruption of the pathogenic biofilm by non-surgical mechanical debridement using antimicrobial and sometimes anti-inflammatory adjuncts, and, as with all biofilm-mediated oral disease, patient-specific instruction in daily plaque removal.
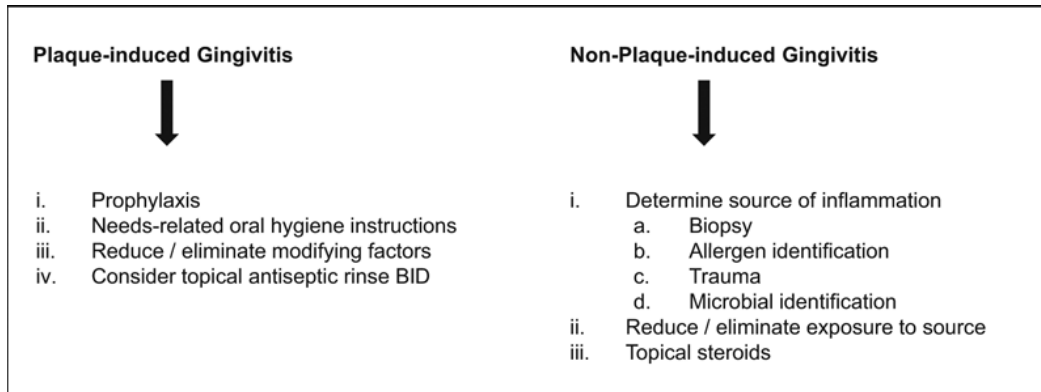
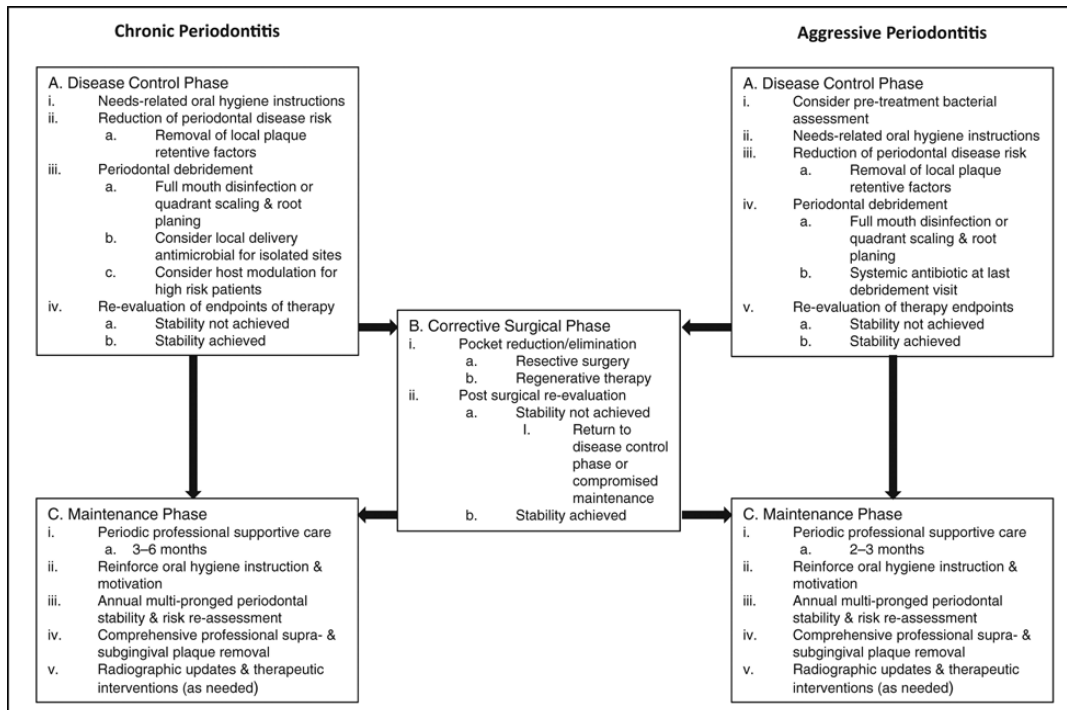*Figure 5. Common treatment strategies for gingivitis. BID: twice a day.*

Figure 6. Comparison of active treatment strategies for chronic and aggressive periodontitis.

While traumatic occlusion is not an etiological factor for periodontal disease, it is considered to be a potential disease modifier. It is often addressed during initial therapy.[5] Management of other potential disease modifiers, such as psychological stress, osteoporosis and poor dietary habits, is often advocated. Such interventions can be beneficial. However, little research has been performed to clarify the effects of these other potential risk indicators on disease susceptibility, and even less research has been performed regarding intervention.[155]

Success in the cause-related phase is achieved when disease progression is halted or significantly reduced, as determined by measurements taken upon re-evaluation (Table 6). Important clinical benchmarks for assessment of treatment success include reduction in bleeding on probing and probing depth, together with gains in clinical attachment levels and optimization of needs-related plaque control. There is insufficient evidence to support the utility of microbial diagnostics as a tool in the management of chronic periodontitis, although microbial assessment may play a useful role in guiding

therapy for aggressive periodontitis and phenotypes of disease that are non-responsive to conventional therapy.[237]

Table 6. Prediction of periodontal stability defined as a change in clinical attachment level of 0 ± 1 mm and no change in radiological bone level

Predictor	Level	Decision criterion	Long-term stability	Reference
Diabetes (HbA$_{1c}$)	Patient	HbA$_{1c}$ ≥ 9% (poor control)	Unfavorable	388
Obesity (BMI)	Patient	BMI ≥ 30 kg/m^2	Unfavorable	310
Smoking	Patient	Current smoker	Unfavorable	258, 316, 396
Oral hygiene (HI)	Full mouth	HI>30% consistently	Unfavorable	41
Radiographs	Site	Crestal lamina dura consistently present	Favorable	322
	Site	Loss in crestal bone height	Unfavorable	322
Bleeding on probing	Site	Bleeding on probing = 0 consistently	Favorable	185, 220
	Site	Bleeding on probing > 0 consistently	Questionable	41, 76, 219
	Full mouth	Bleeding on probing > 30% consistently	Unfavorable	185
Gingival inflammation (GI)	Tooth	All tooth sites GI ≤ 1 consistently	Favorable	222
	Tooth	All tooth sites 1 < GI ≤ 2 consistently	Questionable	222
	Tooth	All tooth sites GI ≥ 2 consistently	Unfavorable	222

Predictor	Level	Decision criterion	Long-term stability	Reference
Probing depth (PD)	Site	Change in PD = 0 ± 1 mm	Favorable	[41], [75], [76]
	Site	Change in PD ≥ 2 mm since previous visit	Unfavorable	[41], [75], [76]
	Site	Eight or more sites with PD ≥ 5 mm	Unfavorable	[76], [258]
	Site	PD ≥ 6 mm	Unfavorable	[258]

For definitions of long-term stability criteria, see.[215]

The surgical/corrective phase of therapy is performed only after thorough re-evaluation of initial therapy has suggested that residual infection/inflammation exists, and compliant patients are still at risk for disease progression (Fig. 6). In the surgical phase of therapy, periodontal regeneration or resection may be attempted, depending on the bone and soft-tissue architecture. Useful treatment algorithms have been published recently and will not be detailed here.[190] A combination of resective and regenerative procedures is often used at a single surgical site (Fig. 7). However, surgical therapy is best avoided in patients whose plaque control is inadequate[228], [287] or who are heavy smokers.[316]

Figure 7. Periodontal surgical intervention for severe chronic periodontitis that combines resective and regenerative strategies to reduce pocket depth and achieve a healthy and maintainable periodontium. (A) Chronic periodontal abscess showing exudate on palpation of teeth 24 and 25. (B) Probing confirms a 12 mm mucogingival/osseous defect. (C) Pre-treatment periapical radiograph showing advanced bone loss. (D) Surgical flap after defect and root debridement and prior to bone graft and Emdogain®. (E) The tissues have been positioned apically and sutured. (F) Probing depths are stable and maintainable. (G) Healthy but receded gingival tissues are seen five years after treatment. (H) Periapical radiograph suggesting some improvement in bone level after 5 years.

The supportive or maintenance phase of therapy involves secondary prevention of periodontal disease.[3] Ideally, this phase is entered only after all signs of disease have been eliminated or substantially reduced and the long-term stability of periodontal health is highly probable. A multi-pronged approach to regular reassessment of periodontal health during the supportive phase is critical to long-term success in preventing disease recurrence (Table 6).[100] Although absence of bleeding on probing is a useful indicator of health,[220] increasing pocket depth over time, or pockets deeper than 6 mm coupled with consistent bleeding on probing, are still the best predictors of disease progression.[41, 75, 258] These measures have been proven useful and are easy to record, and so have become important clinically.[398] Recently, Offenbacher et al.[291, 292] proposed what they call the 'biofilm–gingival interface classification', based on classic clinical disease markers coupled with microbial and host molecular markers for disease, to describe different biological phenotypes of periodontitis. The molecular markers may turn out to be useful adjuncts to the standard clinical markers of probing depth and bleeding on probing.

Efforts continue in the hope of developing saliva- or crevicular fluid-based diagnostic systems that may help to distinguish between health and disease based on microbial or host inflammatory markers.[54] As yet, no system is in wide use, perhaps due to the fact that detailed multi-pronged clinical observations continue to be very effective.

Non-surgical cause-related treatment

Plaque control

The first step in treatment of any form of periodontitis is training the patient in proper plaque removal. Although effective oral hygiene provides limited but positive changes in signs of disease, such as reductions in probing depths and bleeding on probing,[39, 40, 67, 238] optimal daily plaque control is the most important determinant for long-term success in periodontal therapy.[35, 38, 354] A systematic review on the effects of a prophylaxis combined with a single episode of oral hygiene instruction emphasizing use of a manual toothbrush demonstrated a small but consistent reduction in gingivitis, even though it was clear that plaque reduction in these studies was not optimal.[405] More focused training in needs-related plaque removal, such as flossing, the use of woodsticks or other interdental hygiene aids, can be extremely effective in reducing disease long-term when combined with regular professional mechanical cleaning.[33, 34, 38, 210] Combining interdental plaque removal with an already existing habit of toothbrushing has been strongly advocated.[37]

Powered toothbrushes have been shown in systematic reviews to provide a modest additional short-term benefit over manual toothbrushing.[330, 359] Compliance is an issue over the long-term, and even the best powered brushes have yet to demonstrate clinically relevant proximal plaque removal. It is clear that repeated instruction and motivation on interdental cleaning by any means is necessary for long-term success, particularly in the high-risk posterior teeth.[369, 370] When interproximal soft tissue has receded, use of interdental brushes is of particular value.[72, 197, 409]

Removing plaque-retentive factors

The removal of plaque-retentive factors as part of initial periodontal therapy is clearly important. Multiple retrospective cross-sectional studies as well as short-term longitudinal studies have confirmed the negative microbiological and clinical effects of subgingival and otherwise non-ideal restoration margins.[294]

Scaling and root planing

Mechanical root cleaning as a treatment for periodontitis has been advocated for centuries, and scaling and root planing is still the 'gold standard' treatment for chronic periodontitis. This cause-related approach is aimed at removal of pathogenic biofilms, toxins and calculus, and re-establishment of a biologically acceptable root surface. Shrinkage of the periodontal pocket occurs as a combination of soft tissue reattachment to the clean root surface and recession of the soft-tissue margin as a result of a decrease in the inflammatory infiltrate in the periodontal tissues.[39, 40] Significant reductions in the levels of motile rods and spirochetes are a common finding in areas that show clinical improvements after treatment.[142, 161, 327] Evidence for clinical improvement includes positive changes in tissue color, contour and consistency, as well as in reductions of bleeding on probing and pocket depth, and gain in attachment.

Badersten et al.[40] proposed that, for non-molar teeth, there is no true threshold pocket depth where non-surgical periodontal therapy becomes ineffective. However, others have suggested that the ability to adequately remove biofilm and calculus to achieve a biologically acceptable root surface depends on the depth of the pocket, the root anatomy, the instrumentation, the experience of the operator and the approach used.[57, 61, 62, 106, 116, 374] Systematic reviews have indicated that powered instruments, such as

magnetostrictive and piezoelectric ultrasonic scalers and sonic scalers, are at least as effective as curettes in mechanical debridement, but the powered instruments tend to be more efficient.[402, 414] There is some evidence that powered instruments may be more effective in areas that are difficult to access, such as furcations and deeper pockets.[50, 256] When used properly, the powered instruments appear to remove less root structure.[346]

Adjunctive treatments during initial-phase therapy

Systemic antibiotics

Use of systemic antibiotics as an adjunct to scaling and root planing has become the standard of care in aggressive and non-responsive forms of periodontitis. However, the decision to use a systemic antibiotic must be made based on the patient's medical and dental history. Performing microbial culture and obtaining antibiotic sensitivity data are recommended.[8]

Systemic antimicrobials have also shown some benefit with regard to clinical attachment level gains in short-term treatment studies of chronic and aggressive periodontitis, with the benefit being more pronounced in deeper sites.[141, 142] However, as mechanical treatment alone is quite often effective, and development of antibiotic-resistant bacterial strains is a growing problem, widespread use of such adjunctive therapy for chronic periodontitis cannot be justified.[141, 411] Many systemic antimicrobials and combinations of agents were tested in clinical trials, with tetracyclines, metronidazole and combinations of metronidazole with amoxicillin being most frequently reported.[141] Systemic use of antibiotics as an adjunct to non-surgical periodontal therapy may have at least a short-term positive effect on systemic levels of inflammation.[352] and on glycemic control in diabetics.[138]

Local antimicrobial treatment

The delivery of high levels of antimicrobial directly to the disease site has advantages over systemic antibiotics, including fewer side-effects and non-compliance issues. Several systems have been approved by the Food and Drug Administration for use in the USA, and in other countries. By and large, systems showing ease of use, consistent retention at the site of placement, and slow, steady release of high concentrations of antimicrobial have become popular adjunctive therapies. Non-setting gel preparations have fared poorly, presumably due to unfavorable release characteristics.[87, 392] Several large randomized, multi-center clinical trials have demonstrated modest short-term clinical benefits of antimicrobials as an adjunct to scaling and root planning.[107, 109, 179, 419] Test agents with favorable pharmacodynamics included tetracycline fibers, chlorhexidine chips, minocycline microspheres and doxycycline gel. Their use in the initial stage of therapy has shown statistically significant improvements in probing depth reduction, and clinical attachment level gains in some cases. However, reviews have suggested that the magnitude of the changes is of questionable clinical relevance.[52, 88, 133, 144] Moreover, the cost/benefit ratio remains unproven.[99, 158] Currently, the most accepted indication for local antimicrobial treatment is in chronic periodontitis patients with isolated pockets of moderate disease that have not responded to mechanical therapy alone (Fig. 6).[11]

Recent trials using locally delivered minocycline microspheres as part of 'intensive periodontal therapy' demonstrated short-term alterations in several systemic inflammatory markers in addition to providing local clinical benefits that lasted for several months.[92, 399]

Host modulation

The concept of modulating the inflammatory response as a way to reduce or prevent periodontal breakdown has been investigated since Golub et al. observed that minocycline inhibited collagenase activity in a germ-free rat model.[129] As periodontal bone and attachment loss are the result of destructive inflammation, it stands to reason that a reduction of the host response should provide a

useful adjunct to typical mechanical and chemical antimicrobial approaches during disease control or maintenance phases of treatment (Fig. 6). Host modulation approaches have been based primarily on damping down effector molecules such as matrix metalloproteinases and prostanoids, although more recent efforts to inhibit destructive inflammation have targeted upstream mediators, such as p38 MAPK (203), as well as novel downstream lipid mediators, lipoxins and resolvins, that actually appear to resolve the chronic inflammatory response rather than simply suppress it.[148, 407, 408] An additional approach, focused on alterations of bone metabolism by bisphosphonates, has also been studied.[124]

While studies of non-steroidal anti-inflammatory drugs, bisphosphonates, and most recently p38MAPK inhibitors, lipoxins and resolvins, have shown proof of concept, only low-dose doxycycline has obtained US Food and Drug Administration approval for treatment of periodontal disease. In several large, randomized multi-center clinical trials, investigators demonstrated modest clinical benefits with adjunctive low-dose doxycycline after scaling and root planing in subjects with moderate to severe generalized chronic periodontitis.[64, 286, 317] In addition, a systematic review concluded that adjunctive use of low-dose doxycycline, together with non-surgical scaling and root planing, provided a statistically significant improvement over non-surgical therapy alone.[325] However, the clinical relevance of the adjunctive benefits demonstrated for this therapy has been questioned.[133] Moreover, compliance is always an issue when patients are required to take frequent medication for prolonged periods of time, and a modified version of low-dose doxycycline (40 mg everyday) was introduced in response to such issues.[319] Controversy remains regarding the effect of low-dose doxycycline in smokers.[280, 318] From a microbiological viewpoint, there is a growing body of evidence suggesting that the standard regimen low-dose doxycycline (20 mg twice a day) has no detrimental effects on the commensal flora of the oral cavity or the gastrointestinal tract.[391, 412, 413]

However, caution remains regarding application of low-dose doxycycline. Matrix metalloproteinases are ubiquitous and necessary for normal physiological processes, and the potential consequences of long-term matrix metalloproteinase inhibition on other systems are not yet clear. Host modulation therapeutic agents under development show promise, but a magic bullet isn't on the horizon.[202, 203, 408] Further advances in this area of therapy await better classification of diseases and identification of the multi-faceted molecular basis for the biofilm/host imbalances that produce destructive inflammation. A glimpse into the future was provided by the observation that use of resolvins, but not aspirin-triggered lipoxins, have a positive effect on human neutrophils from subjects with localized aggressive periodontitis, and that topical resolvins reverse periodontal inflammation in the rabbit periodontal disease model.[148] Scientists have expressed great hope in pharmacogenomics,[121] in which the individual genetic and epigenetic make-up of the patient will guide efforts to modulate the host response via drugs and even diet. DNA microarray analysis will be useful in this endeavor.[209] Using these molecular approaches, we may finally begin to develop individualized therapies with predictable outcomes for various periodontal diseases.

Full-mouth disinfection

The concept of same-day full-mouth 'disinfection' (antisepsis) was introduced in 1995[320] as a potentially more effective non-surgical periodontal therapy than the conventional quadrant-by-quadrant scaling approach. Many follow-up studies have been performed, with varied results.[25, 26, 205, 273] The idea of radically reducing the levels of bacterial pathogens from all intra-oral niches, including the gingival crevice and periodontal pockets, is conceptually sound. However, variations in study designs have prevented a clear answer as to whether the concept will effectively translate into a widely accepted clinical approach. The pertinent evidence was assessed at the 6th European Workshop of Periodontology. The reviewers concluded that full-mouth scaling and root planing with or without adjunctive antiseptics does not provide significant clinical benefit beyond conventional, staged

debridement. It was concluded that any of the three treatment approaches are valid ways to accomplish debridement in the cause-related treatment phase for chronic periodontitis.[337]

Lasers

The use of laser light to disinfect the periodontal pocket more efficiently has been another area of intense research.[22, 90, 393] A recent review of the available evidence[80] concluded that results are inconsistent, and that the radiation parameters and techniques have not been reported in enough detail to make useful recommendations. According to Schwartz et al.,[349] use of the Er-YAG laser as a monotherapy may be useful in the cause-related phase of therapy, as it appears to provide similar clinical outcomes to conventional mechanical debridement, but the evidence is weak. Other lasers such as the CO_2, Nd:YAG and Nd:YAP lasers have higher potential for thermal damage to the root surface, and have not shown a clinical benefit, and as such are not recommended.[337] The technology appears to require more development and testing before it can be considered a substitute for classic mechanical debridement.[80]

Photodynamic therapy is another technology of great potential.[184] The essence of photodynamic therapy is to load bacteria with a photoreactive dye, such as toluidine blue, and subsequently expose the dye–bacteria complex to tissue-penetrating light. The combination of dye and light energy leads to formation of singlet oxygen reactive species that can cause cell death. Photodynamic therapy could be an interesting adjunct to scaling and root planing, but this approach is still in development.[23, 97]

Surgical phase of treatment

When therapeutic targets are not achieved following appropriate cause-related treatment, a surgical approach may be indicated (Fig. 6). Several surgical procedures have been well documented as a means to gain access to facilitate instrumentation of the root surfaces, reducing pocket depths and restoring clinical attachment. These surgical approaches have been utilized in treatment of periodontal disease for decades, and are broadly classified as access, resective or regenerative procedures. The pocket depth and bone architecture will dictate which surgical approach is indicated.

Access treatment

There have been vigorous debates over the past century concerning the relative merits of surgical and non-surgical treatment for periodontitis.[128] In the 1980s, several groups published longitudinal clinical trials comparing scaling and root planing to various surgical procedures with or without osseous re-contouring. In general, the non-surgical treatments compared reasonably well to more invasive approaches when surrogate outcomes, such as change in probing depth and clinical attachment level, were used.[186-188, 228, 308, 321] Unfortunately, the vast majority of these trials used a split-mouth design, which has serious deficiencies, including carry-across effects.[101, 170, 225] This design is no longer recommended for comparative efficacy studies of periodontal treatments.

A more recent 12-year, randomized, parallel-group clinical trial compared scaling and root planing to surgical access. It showed that surgical access resulted in fewer teeth being lost over time as well as fewer subjects showing continued disease progression. This was particularly evident over the first three years of the study.[354] Over this period, approximately 80% of the subjects who received only scaling and root planing reached a stable endpoint, while 20% continued to show signs of significant clinical attachment loss. However, recognizing the 20% of patients who do not reach a stable endpoint after non-surgical therapy remains a formidable challenge for the clinician. In addition, the study only assessed single-rooted teeth,[354] and did not consider the more difficult furcation areas in multi-rooted teeth.

Resective procedures

Resective procedures are designed to reduce or eliminate periodontal probing depths and establish favorable gingival and osseous contours that will allow more efficient oral hygiene and periodontal maintenance. Two soft tissue resective procedures that have been employed in periodontal treatment for many years are gingivectomy and gingivoplasty.[89, 105, 410] Both have been shown to be effective for reducing probing depths and contouring enlarged gingival tissues. However, these surgical techniques are limited to areas where only soft-tissue contours need to be addressed. They are not indicated when access to or modification of underlying bone contours is necessary.

As a result of the limitations of gingivectomy, use of mucogingival flaps became favored, and is more conducive to gaining access, pocket reduction and elimination of osseous defects. Resective mucogingival flaps described in the literature include apically positioned flaps with and without osseous re-contouring.[119, 183, 288, 345] Studies have demonstrated that the effects of apically positioned flaps with and without osseous resection are predictable in terms of pocket reduction and long-term stability. In a systematic review of randomized controlled trials comparing surgical to non-surgical therapy, it was observed that surgical therapy consistently provided greater pocket depth reduction and clinical attachment gain at deeper sites (≥6 mm pocket depth) compared to non-surgical therapy.[154]

Even back in the 1950s, it was a concern that deeper pockets might leave a nidus for re-infection. This was corroborated by more recent findings that periodontal pathogens such as *P. gingivalis* and spirochetes are more prevalent in deeper pockets,[198, 272] and subjects with a higher prevalence of deeper pockets have a tendency to show greater disease progression over time.[76, 258] Compared with non-surgical therapy, osseous resective and modified Widman surgical procedures result in a reduction of probing depths and clinical attachment gains for periods from one to 12 years.[48, 187, 354]

When periodontal resective procedures are utilized in the treatment of Class II and III furcations, long-term success is uncertain. Treatment of furcated teeth is challenging. As a result, they are likely to lose more attachment than non-furcated teeth. Surgical techniques that have demonstrated long-term success in treatment of furcated teeth include root resection,[143, 332] tooth hemisection and tunneling;[143, 156] however, root caries is a frequently seen reason for failure. With the increased use of dental implants, these types of resective therapies are performed much less often.

Regenerative procedures

Regeneration, not repair, is the optimal treatment outcome for patients with significant bone and clinical attachment loss. However, obtaining predictable regeneration is challenging. An early surgical modality that resulted in periodontal regeneration was the use of bone grafts[343] for treating periodontal infra-bony defects. Over the years, numerous grafting materials have been reported to have potential for true regeneration, including autogenous intra-oral and extra-oral grafts[333, 344] and allografts (Fig. 7).[159, 353] This property is due to their osteogenic, osteoinductive and osteoconductive properties. However, alloplastic grafting materials such as tricalcium phosphate,[55, 371] porous[194-196] and non-porous[425-427] hydroxyapatite, xenografts and composites have been shown to have limited regenerative potential, and act mainly as a filler.[9]

Guided tissue regeneration and biological agents

The concept of selectively isolating the epithelium and gingival connective tissues by use of resorbable and non-resorbable barrier membranes[56, 131, 132, 244, 312, 313, 372, 373] to allow re-population of cells from the periodontal ligament, cementum and bone[259] has led to clinical techniques described as guided tissue regeneration. The literature suggests that when treating two- or three-wall osseous defects, as well as Class II furcations, clinical results are achieved using guided tissue regeneration that are more predictable and durable than simple access flap surgery.[260] Systematic reviews have confirmed the

clinical benefits observed for bone grafting and/or guided tissue regeneration in both intra-bony defects and buccal Class II furcation involvements.[277, 328] In addition, specific flap designs such as the modified papilla preservation technique[85] and the simplified papilla preservation technique in areas with narrow inter-dental papillae have improved regenerative results due to better flap adaptation, tension-free closure and wound stability post-surgically.[86, 394] For technically demanding multi-tooth recession defects, use of a coronally positioned flap via a tunneling procedure is widespread.[21] As for any surgical approach, intensive post-operative care influences the outcomes of these regenerative procedures.

Recent advances in understanding of the wound healing effects of growth factors and biological mediators,[311] such as platelet-derived growth factor-BB, insulin-like growth factor,[123, 241, 242, 341] enamel matrix derivative (e.g., Emdogain®),[153, 350] and bone morphogenetic proteins on the periodontal tissues have given promise to the possibility of obtaining enhanced and predictable periodontal regeneration.[415] Studies utilizing growth factors and biological mediators have demonstrated significant improvement in clinical attachment and periodontal regeneration.[68, 112, 279]

For confined (three-wall) intra-bony defects, there is robust evidence for the use of enamel matrix derivative in promoting tissue regeneration.[400] From animal studies, it appears that there is little benefit of addition of bone grafting materials to enamel matrix derivative or use of a guided tissue regeneration membrane in such three-wall defects and class II furcation defects. However, as the number of bony walls decreases, there is evidence of superior regeneration when a combination of membrane and graft material is used to surgically repair the defect.[351] Much more research must be performed to assess the range of materials available and their most efficient and cost–effective application in various defect architectures.

A systematic review of studies on root conditioning during surgical exposure suggested that such treatment does not result in any significant improvement in periodontal regeneration, and provides little clinical advantage other than removal of a smear layer.[252]

Mucogingival procedures
A significant current focus is on improving oral–facial esthetics, creating an emphasis on mucogingival surgery to enhance the periodontal gingival complex. A more appropriate and contemporary term for such surgery is periodontal plastic surgery. Periodontal plastic surgery is designed to correct the dimensions and amount of gingival tissue in the esthetic zone, provide root coverage lost due to soft-tissue recession, preserve the bone height of an extraction socket, and perform ridge augmentation. A detailed history of these procedures is beyond the scope of this review, and readers are referred to a review on the development of periodontal plastic surgery.[269]

Supportive phase of treatment
Following completion of active periodontal therapy, it is essential that a periodontal maintenance schedule be established. Studies have shown that tooth loss in periodontal patients is related to the frequency and quality of their maintenance care.[38, 420] In addition, periodontal surgical therapy may fail in patients who are seen at infrequent maintenance intervals.[103, 287] A recent systematic review confirmed that patients who are seen at regular intervals for supportive periodontal therapy experience less attachment loss and lose fewer teeth.[122] Therefore, it is very important for each periodontal patient to receive comprehensive periodontal maintenance treatment at appropriate intervals after active periodontal therapy as outlined in Table 5 and Fig. 6. The periodontal disease status should be evaluated and communicated to the patient using the same multi-pronged approach to re-assessment as used after active treatment (Table 6). Intervals between periodontal maintenance visits should range from 2–

6   months depending on the patient's disease phenotype and history, among other things. Shorter intervals decrease the likelihood of progression of the disease.[81]

Concluding remarks

Periodontal diseases are arguably among the most ancient and common infectious diseases affecting humans, leading to permanent destruction of the supporting structures of the dentition and ultimately tooth loss. It has been established that dental biofilm ("plaque"), consisting of many microbial species and their products, is an etiological agent of periodontal disease. It is widely accepted that immunological and inflammatory responses to dental plaque via host-parasite interaction are manifested by clinical signs and symptoms of periodontal diseases. The outcome of this interaction can be modulated by other components known as risk factors (modifiers), either inherent (genetic) or acquired (environmental) in nature, significantly affecting the initiation and progression of periodontal diseases of different types. While definitive genetic factors responsible for either susceptibility or resistance to periodontal diseases await definitive identification and verification, a small number of environmental factors affecting the pathogenesis of periodontal diseases have been described. They include, among others, smoking, diabetes, medication, and nutrition.

Currently, periodontal diseases are classified based upon clinically observed disease traits using radiographs and clinical examination: gingivitis; chronic periodontitis; aggressive periodontitis; periodontitis as manifestation of systemic diseases; necrotizing ulcerative periodontitis; abscesses of the periodontium; periodontitis associated with endodontic lesions; and developmental or acquired deformities and conditions. Advances in genomics, molecular science, and personalized medicine may result in guidelines for unambiguous disease definition and diagnosis in the future (Fig. 8). Recent studies have implied that periodontal diseases and several systemic conditions, such as diabetes, cardiovascular disease, and pre-term delivery are interconnected, although concrete relationships still await to be ascertained. Therefore, by answering critical questions about the physiology of host-parasite interactions in periodontal diseases, scientists may be able to generate new information regarding the pathogenesis of systemic medical disorders, and vice versa.

Figure 8. Example of a case of periodontal disease that is not captured by the current classification system. (Top) Intra-oral photographs of a 52-year-old Caucasian male who presented with a low plaque index (10%), low full-mouth bleeding on probing index (<5%), and a lifelong history of hard-bristle toothbrush use. There was no history of scaling and root planing or surgical debridement, and only recent free soft-tissue grafts on teeth 22 and 27 for recession coverage. The overly aggressive hygiene probably accounted for some recession and abrasion. (Bottom) Significant generalized horizontal bone loss is seen in the radiographs. Its etiology is unknown. This may represent a non-inflammatory destructive periodontal disease phenotype[300] modified by traumatic toothbrush abrasion.

The therapeutic efforts for controlling periodontal diseases focus on the removal of dental biofilm from the affected lesion, as active treatment centers on non-surgical mechanical debridement with antimicrobial and sometimes anti-inflammatory adjuncts. The surgical therapy aims at gaining access to the lesion and correcting unfavorable gingival/osseous contours to achieve a periodontal architecture that will provide for more efficient oral hygiene and periodontal maintenance. In addition, recent advances in tissue engineering have provided an efficient means to regenerate/repair periodontal defects, based upon principles of guided tissue regeneration and utilization of growth factors/biologic mediators. To maintain periodontal stability, these therapies must be supplemented by a long-term maintenance program (supportive periodontal therapy).

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