Published in final edited form as:

Front Oral Biol. 2012 ; 15: 160–176. doi:10.1159/000329678.

Paradigm Shift in the Pharmacological Management of Periodontal Diseases

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Abstract

It is becoming clear that variations in inflammatory response are a major determinant in susceptibility to periodontitis. However, our understanding of the relationship of the causal agents in periodontitis to the pathogenesis is not as clear as we once thought, and thus therapies based on etiopathogenesis are similarly in question. We are entering a new era of therapeutic discovery that may have a major impact on our management of the periodontal diseases. Fundamentally, periodontitis is an irreversible condition and once both soft and hard tissues are lost, the healthy periodontal architecture cannot be completely or predictably rebuilt. The discovery of new families of lipid mediators of resolution of inflammation (the lipoxins) and eicosapentaenoic-acid- and docosahexaenoic-acid-derived chemical mediators (the resolvins and protectins) opens new avenues to designing resolution-targeted therapies to control the unwanted side effects of excessive inflammation. The novel protective and therapeutic actions of pro-resolution lipid mediators following microbial challenge are mediated by regulation of the local and systemic inflammatory response that has a direct impact on the organization of the biofilm (plaque) and suggests a new paradigm in clinical periodontal therapeutics.

Periodontal infection is among the most common infections in man, and is considered to be initiated by microorganisms of the dental plaque biofilm [1, 2]. The pathogenesis of periodontal disease has for convenience often been described in terms of an infectious disease that one would ‘catch’ with similarities to other acquired exogenous infections [3, 4]. However, there is currently an inadequate understanding of host-related factors affecting the initiation and progression, and of the impact of environmental determinants of the disease, such that therapeutic interventions have focused on methods to eliminate the ‘pathogenic’ bacteria that were assumed by association to be directly involved in the destruction of the host tissues [5]. Hence, periodontal therapy has focused on the mechanical removal of plaque and its bacterial contents supplemented with a wide range of antibiotic and antiseptic compounds [6, 7]. Mechanical debridement, a widely-used and accepted technique to treat and prevent the future incidence of periodontitis, has been regarded as the ‘gold standard’ treatment, and it is generally accepted that chemical antibacterial treatments alone do not have efficacy in periodontal treatment [8]. Mechanical methods, including nonsurgical and surgical techniques, aim to eliminate bacterial biofilms and prevent regrowth by removing ecological niches [9]. Practitioners of dentistry, and particularly

periodontists, have come to appreciate that permanent eradication of bacteria is not possible [10, 11]. Moreover, with the development of more sensitive techniques for the identification of bacteria [12], it has been hypothesized that the pathogenic biofilm in periodontitis represents an overgrowth of commensal organisms [13]. The parameters that enable the shift in the composition of the biofilm highlight the multi-faceted complexity of periodontal pathogenesis [14]. These insights do not reduce the importance of bacteria and other microorganisms in the etiology and pathogenesis of periodontal disease; however, host-related factors – such as genetics and immune response, diet, smoking, stress, systemic health and social elements – are all known to be major disease determinants [15, 16]. Thus, a fresh and unbiased assessment is required to design novel treatment modalities in complex inflammatory diseases such as periodontitis. This chapter focuses on the shift in emphasis from the periodontal infection to periodontal inflammation as the target for pharmacological interventions for treatment of periodontal diseases.

What Is Unique about Periodontal Diseases?

Anatomically, teeth are the only mineralized structures that traverse the epithelium to be exposed to an extremely contaminated external environment [17]. The soft and hard tissues of the periodontium include various types of epithelium, connective tissue, bone and a resilient attachment of the teeth to these structures (the periodontal ligament). Within this sophisticated organ system, the tooth serves not only as a medium for external stimuli, but its surface is also an environment for accumulation and colonization by a diverse group of bacterial species. Because teeth are always exposed to the external environment, the periodontium is continuously contaminated by bacteria [1]. The interaction between dental-periodontal tissues and colonizing organisms is a lifelong process that begins immediately after tooth eruption. However, considering this exposure, there is relatively little disease; a balance between host and bacteria is generally maintained in this commensal relationship. Periodontal diseases are chronic diseases that result from host-mediated destruction of the supporting tissues of the dentition when this balance is lost or disturbed by genetic and environmental risk factors [18, 19].

Evolution of the Current Treatment Paradigm for Periodontal Diseases

A link between bacteria and disease was discovered as early as the 18th and 19th centuries (germ theory) [20]. This was a major breakthrough in the history of medicine. Koch described the direct link between certain microorganisms and disease by demonstrating that once the associated bacteria were absent, the disease resolved [21]. This observation combined with the discovery of penicillin in the 20th century formed the basis of therapy, and successfully controlled or eliminated major infectious diseases [22]. However, the assumption that there was an antibiotic for every infection was an oversimplification of the complexity of the microbiome and interspecies ecological dynamics of microorganisms. It was soon realized that not all bacterially associated diseases were treatable with antibiotics. The human microbiome comprises more bacterial cells than host cells and the symbiotic balance is central to health. The microbiome is not static; the species change and adapt to environmental challenges, most notably, the emergence of antibiotic resistance [23]. We

continue to define the human microbiome, and we continue to search for effective methods to restore homeostasis between the host and commensal bacteria.

The concept of removal of accretions on the teeth is much older than the germ theory. Elimination of the accumulation of debris on tooth surfaces was associated with good health was recognized by the ancients; Hippocrates recommended that ‘teeth be cleaned with a ball of wool’. While the mechanism of why this was beneficial was not immediately clear to our ancestors, even the first practicing dentists used this approach in the routine prevention and treatment of pyorrhea [24]. Various instruments were developed over time for use by dental practitioners in a professional setting and for patient home use to remove what we now call ‘plaque’ build-up on tooth surfaces [25]. After thousands of years, this is still the most essential component of oral hygiene measures for the prevention of periodontal diseases.

The demonstration that bacteria were causative in periodontal disease was not made until 1960 [26]. Subsequently, the discovery of the association of specific bacterial species with health or disease and detailed characterization of various complexes of bacteria led to current antimicrobial approaches for prevention and treatment of periodontitis. In his pioneering work, Socransky [27] refined Koch’s postulates in the context of periodontitis and established our modern understanding of periodontal infection. Both non-surgical and surgical periodontal therapies have the goal of elimination of periodontal pockets to provide a cleansable environment for the maintenance of a plaque-free dentition [28]. The variety of periodontal therapeutic procedures is beyond the scope of this chapter; the important point is that the bacteria are the target. Various antiseptic, systemic and local antibiotic regimens have been added in conjunction with mechanical techniques to further target the bacteria with considerable success [29]. Nevertheless, periodontitis continues to present a significant health burden in the susceptible population [30].

Not too long ago, it was assumed that periodontitis could be eliminated in modern societies though better methods of plaque control; with time, only under-served populations in the developing world would have significant periodontal disease. Interestingly, in recent years, it has been documented that diseases of aging, including periodontitis, are negatively impacted by increasing obesity, smoking and other behaviors of modern society, and that there are interactions between diseases of aging, including type 2 diabetes, cardiovascular diseases and periodontitis [31–33]. The association of periodontitis with major non-infectious diseases suggests that a better understanding of the host’s role in periodontal susceptibility is necessary.

Role of Inflammation in Periodontal Diseases

Inflammation is a physiologic series of responses generated by the host in response to infection or injury. The initial events of inflammation are initiated by vascular reactions at the site of injury leading to extravasation of fluid and plasma proteins and recruitment of leukocytes to the site of injury [34]. Inflammation is a natural beneficial response confining the injury or infection, and serves as the first step in the initiation of the immune response [35]. Ideally, the innate immune or inflammatory response is sufficient to eliminate the infection, allowing for healing and return to homeostasis. If the innate immune response

fails, chronic inflammation ensues. In the case of chronic inflammation, the persistence of the response leads to host tissue self-destruction and may result in irreversible pathological changes. Various cell types, including mast cells, platelets and leukocytes generate inflammatory mediators (chemokines and cytokines). Elevated levels of these molecules promote inflammation and amplify the response [35]. Proteins – including cytokines and chemokines, low-molecular-weight lipids derived from arachidonic acid, nitric oxide and carbon monoxide, reactive oxygen species, and nucleotides – are recognized as inflammatory mediators [36, 37].

Neutrophils are the most abundant white blood cells recruited to the early inflammatory periodontal lesion [18, 38]. The early response that initiates the inflammatory cascade begins with expression of cell adhesion molecules on endothelial cells and secretion of various cytokines such as IL-8 and MCP-1 in response to the bacterial stimulus that recruits neutrophils to the site of invasion [39, 40]. If the first line of defense fails to clear the bacteria, the lesion matures as described histologically by Page and Schroeder [41]: the established chronic gingivitis lesion exhibiting all the components of an immune lesion with T cells, B cells and antibody-secreting plasma cells. The trigger for transition from the established (stable) gingivitis lesion to the advanced or progressing periodontitis lesion remains elusive, but it is known that it is characterized by a continuous and uncontrolled response by neutrophils. Interestingly, it would appear that in the progressing immune lesion of periodontitis, there is continuous neutrophil activation leading to ‘neutrophil-mediated tissue injury’ [15, 42, 43]. Localized aggressive periodontitis (fig. 1a, b) has been called the ‘Rosetta Stone’ of periodontal diseases providing insights into the pathogenesis of more common forms of chronic periodontitis [38]. The localized aggressive periodontitis lesion is an example of neutrophil-mediated tissue injury in which neutrophils are primed or hyperactivated resulting in elevated basal levels of superoxide generation and an increase in response to secondary stimuli (fig. 1c, d). In chronic periodontitis, the trigger for conversion of the gingivitis lesion to periodontitis is likely related to excessive recruitment of neutrophils followed by excessive release of inflammatory mediators associated with rapid and widespread tissue destruction [42].

Once the conversion of the gingivitis lesion occurs, the neutrophil is a rich source of prostaglandin (PG)E₂ that probably accounts for the majority of PGE₂ detected in the gingival crevicular fluid of periodontitis patients [44]. Levels of PGE₂ in the crevicular fluid of patients with periodontal infections correlate with disease severity and aggressiveness [45].

Lipid Mediators of Inflammation

Initially isolated from peanut (*Arachis*) oil, arachidonic acid has been shown to be a central component of phospholipid metabolism in mammals. It is generated from linoleic acid by the action of a desaturase enzyme system [46, 47]. Biosynthesis of most eicosanoids begins with the cleavage of arachidonic acid from the 2-position of phospholipids in the cell membrane through the action of phospholipase A₂ (PLA₂). Prostanoids and leukotrienes (LT) are produced via the action of the enzymes cyclooxygenase (COX) and lipoxygenase (LO) [49]. COX has two isoenzymes: COX-1 and COX-2, sharing 64% identity and similar

enzymatic activity [48]. While COX-1 is expressed constitutively, COX-2 is activated by ligand-coupled stimulation and alternatively known as the inducible or inflammatory COX [49]. The second major group of eicosanoids comprise the LT and other products of the LO pathways [50]. Three different LO substitute the 5, 12 and 15 positions of arachidonic acid, giving rise to hydroperoxides of eicosatetraenoic acid (HPETE). The 5-LO, 12-LO and 15-LO are found in neutrophils, platelets and endothelial/epithelial cells, respectively, and their products are named accordingly (5-HPETE, 12-HPETE and 15-HPETE) [51–54].

Resolution of Inflammation

Since many molecules in eicosanoid metabolism are associated with proinflammatory outcomes, blocking the actions of arachidonic acid cascade products has been the major pharmacologic target for blocking inflammation. Many drugs have been developed to arrest or modify inflammation by inhibiting the enzymatic pathways or blocking the receptors that lead to the generation of lipid mediators. One action of corticosteroids is thought to be inhibition of PLA₂ blocking the release of arachidonic acid from membrane phospholipids [55]. This nonspecific inhibition of eicosanoid generation, although highly effective, is not without side effects leading to multiple adverse outcomes including suppression of the acquired immune system. Nonsteroidal anti-inflammatory drugs or specific COX-2 inhibitors have been used to block PG production [56–60] specifically by suppressing COX-mediated inflammation without blocking acquired immunity [56]. However, these agents also lead to significant side effects, due to their lack of selectivity, blocking both the constitutive (COX-1) and the inducible (COX-2) isoforms. There is considerable controversy in the clinical literature about the unwanted side effects of COX-2 inhibitors in the gastrointestinal and cardiovascular systems [61–63].

A major discovery by Serhan et al. [64] changed the prevailing concepts relating to the resolution of inflammation. Since the first descriptions of inflammation in ancient times to the late 20th century, it was always assumed that the inflammation passively resolves following the degradation or loss of proinflammatory mediators. Recent work shows that resolution of inflammation is an active process mediated by a newly identified class of eicosanoids produced by the actions of two different LO enzymes on a single arachidonic acid molecule. The product of this LO:LO interaction is a new class of molecule called lipoxins (LX) [65]. Several different pathways can generate LX. In general, interactions between cells result in the generation of LX, while single cells can also produce these compounds [66]. For example, arachidonic acid is substituted at the 15 carbon by endothelial cells and the resulting 15-HPETE is further acted upon by neutrophil 5-LO; the 5,15-HPETE is rapidly converted by hydrolases to either LXA₄ and/or LXB₄ [67–69]. LX are receptor agonists whose major functions include the arrest of neutrophil activity (migration and secretion), induction of neutrophil apoptosis, and the non-phlogistic recruitment of monocytes and macrophages. Non-phlogistic, or literally, non-fever-producing macrophages secrete no proinflammatory cytokine, but exhibit enhanced phagocytosis of bacteria and apoptotic neutrophils [37, 64, 70–73].

The neutrophil's role in LX generation is crucial. When stimulated by various agonists, neutrophils release 15-HETE, which is further transformed into LX. This pathway suggests

that precursors of LX synthesis can be stored within the membranes of inflammatory cells and then released by stimuli activating PLA₂. The second major route of LX biosynthesis is mediated by the interaction of human neutrophils with platelets in blood vessels. Cell-to-cell interaction involves 5-LO in neutrophils and 12-LO in platelets for the insertion of molecular oxygen into arachidonic acid [74]. When platelets adhere to neutrophils, they convert LTA₄ into a cation (carbonium) by 12-LO [75] and produce LXB₄ or LXA₄ functioning as a 'LX synthase' in platelets [75]. Platelet-neutrophil adherence and transcellular biosynthesis are important anti-inflammatory events that regulate neutrophil recruitment by initiating the formation of lipid mediators that limit proinflammatory responses.

Aspirin also plays an important role in the generation of LX [72]. COX-2 inhibition by aspirin is by acetylation of COX-2, which generates a new still-active enzyme, 15R-LO. The enzymatic product is 15-R-HETE instead of PG, which forms the epimer 15-R-LX (aspirin-triggered LX, ATLa). ATLa is more potent than native LXA₄ in inhibiting neutrophil adhesion and cell proliferation [76]. COX-2 is increased in inflammatory reactions and in disease states, including colon cancer, and normalized upon aspirin intake [77–79]. These actions are linked to ATLa that serve as endogenous anti-inflammatory signals that mediate some of aspirin's beneficial actions [77]. Aspirin also impacts COX-2-bearing vascular endothelial cells or epithelial cells and their coactivation with neutrophils [72].

Potential Role for Lipoxins as Therapeutics

While it is well appreciated today that neutrophils play an essential role in host defense, their prolonged activation can lead to tissue injury observed in common chronic inflammatory diseases. Because of the importance of leukocyte trafficking, endogenous positive and negative signaling mediators of inflammation have been referred to as local 'go' and 'stop' signals [35, 66, 80–84]. LXs are an important stop signals [85] produced in vivo during the course of inflammation [86–89]. Alterations in LX levels may be linked to the pathophysiology of several human diseases and may have specific local functions. The first demonstration of LX in clinical inflammation was in bronchial lavage. LXA₄ and LXB₄ are formed in nasal polyps and LXA₄ is generated in nasal lavage from aspirin-sensitive asthmatics and in experimental nephritis [90]. Rupture of atherosclerotic plaque leads to rapid generation of LXA₄ in the intracoronary artery [91]. LXs are also generated by normal human bone marrow, and during chronic myelocytic leukemia platelets lose 12-LO, losing the ability to generate LX, and this may be related to blast crisis [92]. In humans, the aspirin-tolerant subjects generated both LXA₄ and ATL, but aspirin-intolerant patients proved to have a diminished capacity to generate ATL and LX upon aspirin challenge [93]. In an experimental periodontitis rabbit model, animals are protected by LXA₄ and transgenic rabbits over-expressing 15-LO generate enhanced levels of LX, exhibit a reduced inflammatory phenotype, and are protected from bone loss in periodontal disease [94] (fig. 2).

Resolvins as Pharmacological Agents in Therapeutic Intervention of Periodontal Diseases

Dietary fatty acids, particularly the ω -3 polyunsaturated fatty acids (ω -3 PUFA), are known to clinically reduce inflammation in humans. Mammals do not produce the major ω -3 fatty acids found in fish oil: eicosapentaenoic acid (EPA) and its derivative docosahexaenoic acid (DHA). EPA and DHA are held to be beneficial in a wide range of human inflammatory disorders, including cardiovascular diseases, rheumatoid arthritis, Alzheimer's disease, lung fibrosis and inflammatory bowel disease, as well as periodontal disease [95–99]. These essential fatty acids and their precursor, the vegetable oil α -linoleic acid, are widely believed to act by prevention of conversion of arachidonate to proinflammatory eicosanoids or serving as an alternative substrate producing less-potent products. Novel oxygenated products of ω -3 PUFAs generated by enzymatic pathways similar to the production of LX are called 'resolvins', and exhibit potent actions in the resolution of inflammation. Similar in action to LX, resolvins are endogenous mediators produced from exogenous or dietary fatty acids [70, 100]. The specific members of the resolvin family (resolvin E and D series) have potent biological actions demonstrable in the nanomolar to picomolar range in vitro and in vivo [64, 100–104]. The receptors for resolvins or the E series are the chemR23 receptor expressed on macrophages and BLT1 on neutrophils [105], which are distinct from the LX receptor (FPRL1). These pathways account for, in large part, the systemic anti-inflammatory activity of ω -3 PUFA in the diet [95, 106–108]. Similar to LX, when aspirin is introduced, ω -3 PUFA are metabolized into new resolving molecules that are more stable and therefore longer acting [100] (fig. 3).

Paradigm Shift in the Pharmacologic Management of Periodontitis

Homeostasis is a fundamental characteristic of living things. It is the maintenance of the internal environment within tolerable limits, and is often described as a process of balance. Physiologic resolution of a well-orchestrated inflammatory response is essential to maintain homeostasis at the cellular and tissue levels [109]. Acute local inflammation in healthy individuals is self-limiting, and resolves by means of an active series of termination events [110]. When an inflammatory event is terminated, the complete clearance of invading leukocytes from the inflammation site is required. Complete return to homeostasis cannot occur while neutrophils remain in the lesion. If the process is incomplete, there is destruction of the cellular matrix and scarring and fibrosis can occur, resulting in incomplete healing or persistent (chronic) inflammation [34]. In many inflammatory conditions, such as periodontitis, incomplete neutrophil clearance can impact the conversion of an acute gingivitis to chronic periodontitis [18]. Scarring or fibrosis during periodontal healing prevents the return to homeostasis, which causes failure of regeneration of the periodontal tissues.

The potential of pro-resolving molecules such as RvE1 for the treatment of established periodontitis was explored using a rabbit model (fig. 4). In the RvE1-treated group, inflammation was completely eliminated; pocket depth was returned to normal and soft tissues returned to healthy levels and appearance (fig. 5). Restoration of crestal bone height, elimination of infrabony defects, and regeneration of new cementum, connective tissue and

bone with an organized periodontal ligament were signs of complete regeneration of tissues to pre-disease levels [111]. Periodontitis was also shown to have a systemic impact elevating the levels of IL-1 β and CRP in all animals. Oral topical RvE1 therapy reduced systemic IL-1 β and CRP levels. Rabbits treated with RvE1 showed an essentially complete recovery without any signs of local and systemic inflammation [111] suggesting a complete return to tissue homeostasis.

Conclusion

Inflammation is a protective host response to infectious challenge and tissue injury that, if unregulated, can lead to loss of tissue structure as well as function. Inflammation is a self-limiting and self-resolving system with endogenous regulators and counter-regulatory mechanisms. Failure of regulation of inflammation leads to uncontrolled responses and tissue damage. Restoration or regeneration of tissues lost to disease is problematic in many human diseases, such as arthritis and periodontitis. Therapies that are aimed at regeneration of lost tissues attempt to recapitulate development. Hence, tissue engineering strategies add back growth factors, substrates and other molecules to mimic development. In the context of periodontitis, the discovery and development of pro-resolving agents emphasizes the role of local inflammation in tissue regeneration. Endogenous anti-inflammatory and pro-resolving compounds and pathways are important in resolution, catabasis, and the metabolic, cellular and tissue events leading to a return to homeostasis, but also have therapeutic potential for the treatment of inflammatory diseases. The potential use of LX, resolvins and protectins opens new avenues for the design of resolution-targeted therapies to control unwanted side effects of aberrant inflammation.

The pharmacologic use of potent ‘resolution agonists’ to orchestrate the return of the tissue to homeostasis and rescue resolution deficits has a net advantage over the traditional anti-inflammatory by controlling excessive cellular activity, but also enhancing clearance of bacteria and dead cells. Available data and the results of ongoing studies demonstrate that natural pathways of resolution can be used to limit inflammation and promote healing and regeneration with a minimal risk of side effects [86, 100, 106, 112].

Periodontal disease is an important disease, not only because it is one of the most common diseases of man, but because within it, various aspects inflammatory disease progression can easily be studied. Studies that elucidate the pathogenesis of periodontal disease will add to our understanding of inflammatory disease in general. Within this context, lipid mediators not only present an exciting area of research, but also have potential for the development of novel treatment strategies. Understanding the role of pro-resolving molecules in regulating inflammatory processes and responses will also provide new insights into our understanding of the link between local and systemic diseases. Since the integrated response of the host is essential to health and disease, it is important to achieve a more complete understanding of the molecular and cellular events governing the formation and actions of endogenous mediators of resolution that appear to control the magnitude and duration of inflammation.

Acknowledgments

This work is supported in part by USPHS DE15566, DE19938 and DE16191.

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Fig. 1.

Localized aggressive periodontitis (LAP) is characterized by severe and localized bone loss around first molar and incisor teeth. **a** Schematic depiction of periodontal structures in LAP. **b** Clinical appearance of bone around molar teeth after the gingival flaps are elevated during periodontal surgery clearly shows the extent of localized destruction. **c** LAP neutrophils present a primed phenotype as shown by elevated basal levels of superoxide generation that lead to further excessive response to secondary challenge. * $p < 0.05$. **d** In response to LXA₄ treatment, agonist-induced superoxide generation is significantly inhibited in neutrophils from non-LAP healthy individuals that were chosen as matched controls, while LAP neutrophils do not respond to LXA₄ suggesting a failure of resolution pathways. * $p < 0.05$.

Fig. 2.

LXA₄ prevents periodontal inflammation and bone loss induced by *P. gingivalis* in the rabbit periodontitis model. **a** As opposed to other animal models of periodontitis, ligature placement alone does not cause any change in alveolar bone. **b** In response to experimental periodontitis induced by *P. gingivalis* and ligature placement, local severe bone loss is observed. **c** Topical LXA₄ treatment simultaneously applied with *P. gingivalis* prevents periodontitis and alveolar bone loss. **d** Histological analysis on HE-stained sections reveals that LXA₄ prevents bone loss. **e** Periodontal disease induced by *P. gingivalis* results in alveolar bone resorption (depicted by arrow). **f** 15-LO transgenic rabbits are resistant to experimental periodontitis.

Fig. 3.

Endogenous lipid mediators of inflammation. Arachidonate, an ω -6 fatty acid, is cleaved from the cell membrane by PLA₂ and becomes the substrate for two major enzyme groups; the cyclooxygenases (COX-1 and COX-2) and the lipoxygenases (5-LO, 12-LO and 15-LO). The products of these enzymes are potent proinflammatory mediators. Late in the inflammatory response, when the cells containing the LO and the LO products are in high concentration, there is a crossover of LO activity through a process called 'transcellular biosynthesis' or cell:cell (LO: LO) interactions. The resulting products are arachidonate molecules that are substituted at two sites rather than one. The enzymatic products of new double-substituted molecules are termed 'lipoxins' and represent a new class of molecule with distinct receptors and pleomorphic functions depending on the cell type driving the resolution of inflammation.

Fig. 4.

Prevention of periodontitis. In a rabbit ligature model of periodontitis induced by the human pathogen *P. gingivalis*, RvE1 was evaluated for prevention of periodontitis over 6 weeks. **a** Topical application of 4 µg of RvE1 three times per week prevented periodontal inflammation and bone loss, while in the disease group (ligature + *P. gingivalis*), profound inflammation and obvious bone loss was observed (arrow). **b** Direct measurement of alveolar bone loss revealed that RvE1 treatment significantly inhibited bone loss. * $p < 0.05$.

Fig. 5.

RvE1 monotherapy for periodontitis. Periodontitis was induced in New Zealand white rabbits with 3–0 silk ligature and topical application of the human periodontal pathogen *P. gingivalis* for 6 weeks (baseline periodontitis). Established disease was treated for 6 weeks with either RvE1, PGE₂, LTB₄ or ethanol (vehicle). **a** Periodontal disease was obvious with all characteristics of human periodontitis including soft and hard tissue destruction at 6 weeks. **b, c** At 12 weeks, the periodontal disease dramatically progressed in the LTB₄- and PGE₂-treated groups. Bone destruction is clearly seen on the defleshed specimens (arrows). **d** Following 6 weeks of treatment, topical application of 4 µg RvE1 three times per week resulted in restoration of tissues to healthy levels. The bar graph shows alveolar bone loss for all animals directly measured on defleshed jaws. RvE1 treatment resulted in significant bone and soft tissue attachment gain, whereas other treatment groups showed progression characterized by soft tissue and bone destruction. * $p < 0.05$.