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HOST MODULATON THERAPY: A COMPREHENSIVE THERAPY

Periodontology

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ABSTRACT

Periodontitis was believed to be an inevitable consequences of aging and uniformily distributed in population. This age old belief was again supported by another belief that disease severity was directly proportional to plaque levels, but in mid 1990's early insight about complex diseases like periodontitis, led to new conceptual models Of pathogenesis1. In recent years the role of microorganisms as the principle etiological factor in periodontal diseases has gained new perspective. Periocentics or the Use of the pharmacological agents specifically developed to manage host modulation which is an interesting and emerging aid in the management of periodontal disease along with mechanical debridement .Host modulation therapies are being proposed and developed to bring down excessive levels of enzymes , cytokines, prostanoids as well as modulate osteoclast function, Increased application of host modulation therapy in periodontal disease management should be explored to effectively control and prevent the periodontal disease progression

KEYWORDS

INTRODUCTION

Periodontitis was believed to be an inevitable consequences of aging and uniformily distributed in population. This age old belief was again supported by another belief that disease severity was directly proportional to plaque levels, but in mid 1990's early insight about complex diseases like periodontitis, led to new conceptual models Of pathogenesis[1]. In recent years the role of microorganisms as the principle etiological factor in periodontal diseases has gained new perspective.[1]

The basic conceptual model of periodontitis was revised by Page and Kornman, in 1997[2]. According to this model, the microbial challenge presented by subgingival plaque bacteria results in an up-regulated host immune-inflammatory response in the periodontal tissues that is characterized by the excessive production of the inflammatory cytokines (e.g., interleukins, tumor-necrosis factor), prostanoids (e.g., Prostaglandin E_2), and enzymes, including the Matrix Metalloproteinases (MMPs).

These pro-inflammatory mediators are responsible for the majority of the periodontal breakdown that occurs, leading to the clinical signs and symptoms of periodontitis. The process is modified by environmental (e.g., tobacco use), acquired risk factors (e.g., systemic diseases), and genetic susceptibility.[2]

This host immune inflammatory response is essentially protective in intent, to combat the bacterial infection and prevent the ingress of bacteria into the tissues. In the persons who are not susceptible to periodontitis (disease resistant), these primary defense mechanisms control the infection, and chronic inflammation (i.e., chronic gingivitis), may persist indefinitely. However, in disease susceptible individuals, the inflammatory events extend apically, and laterally to involve deeper connective tissues and alveolar bone, thus resulting in periodontitis.

Today our knowledge about the pathogenesis of periodontal disease has gained new perspectives. This understanding has thus opened a new horizon for researchers to explore a novel approach of treatment by means of host response modulation. Host Modulation Therapy (HMT) is a treatment concept that is aimed at reducing tissue destruction and stabilizing or even regenerating the periodontium by modifying or down-regulating the destructive aspects of host response, and up-regulating the protective or regenerative responses. Host modulation therapy offers the potential to move periodontal therapy to the next level.[3]

The concept of Host Modulation was first introduced to dentistry by William et al., 1990, and Golub et al., 1992. In 1990, Williams concluded that "there are compelling data from studies in animals and human trials, indicating that pharmacologic agents that modulate the host responses believed to be involved in the pathogenesis of periodontal destruction may be efficacious in slowing down the progression of periodontitis."[3]

There are various natural inherent defense mechanisms, which have demonstrated to moderate the host response and co-ordinate the resolution of inflammation. Lipoxins, for example, are endogenous molecules, which are liberated as part of host defense during inflammation, and have demonstrated as having inflammation resolving properties, by stopping signals for PMN (polymorphonuclear neutrophils) mediated tissue injury.[3] Similarly, it has been shown that the imbalance between activated matrix metalloproteinases (MMPs) and their endogenous inhibitors (Tissue Inhibitors of Matrix Metalloproteinases or TIMPs), leads to the pathological breakdown of extracellular matrix during periodontitis.[4] Moreover, activities of the pro-inflammatory cytokines (IL-1,TNF-α & interferon-γ), are counter-imbalanced by production of the anti-inflammatory cytokines (IL-4, IL-10 and IL-1 receptor antagonist)[5]

Therefore, it appears logical that drug preparations that mimic these endogenous anti-inflammatory mechanisms may prove to be an effective strategy of periodontal treatment[6]. Thus, host modulation therapy (HMT) is designed to block various pathways which are responsible for periodontal tissue breakdown. Keeping that in mind, specific key mechanisms of host tissue destruction have been elucidated, with the simultaneous identification of critical intervention with host modulating agents. These include the

(a) Regulation of immune and inflammatory responses
(b) Regulation of excessive production of Matrix metalloproteinases
(c) Regulation of the arachidonic acid metabolites
(d) Regulation of bone metabolism

Compared to other treatment approaches host modulation therapy presents as a treatment modality with relatively fewer side effects. Host response modulation therefore offers the potential for down-regulating destructive aspects of the host response so that, in combination with conventional treatments to reduce the bacterial burden, the balance between health and disease progression is tipped in the direction of a healing response. Thus this therapy has opened new avenues for management of periodontal disease.[6]

Thus it can be summarized that periodontopathogens are neccesary to cause periodontal disease . In response to infections or inflammation , two distinct yet intricately linked immune responses occur innate and adaptive. The immune system is essential and body must be marshal the innate and adaptive response in order to stave of infections. However the inflammatory diseases, the response become chronic and tissue do not return to homeostasis[7]. The development of an immune inflammatory response during periodontitis as susceptible individual,results in local production of variety of inflammatory mediators pro-inflammatory cytokines molecules and cytokine network plays the essential role in pathogenesis of periodontal disease.

Periocentics or the Use of the pharmacological agents specifically developed to manage host modulation which is an interesting and emerging aid in the management of periodontal disease along with mechanical debridement .Host modulation therapies are being proposed and developed to bring down excessive levels of enzymes , cytokines, prostanoids as well as modulate osteoclast function[7].

Heasman et al (1993)- Conducted a study and reported that flurbiprofen controls gingival inflammation at both preventive and therapeutic levels in the experimental gingivitis model also and suggested that this effect could be associated with an inhibition in the production of cyclooxygenase metabolites that indirectly affects GCF-LTb_4 levels.[8]

Fieldman et al in (1983) - Conducted a study and reported that the inhibition of bone loss found could be due to the chronic ingestion of ASA or ASA and indomethacin.

Williams et.al (1989)- In a study concluded that the NSAID flurbiprofen, as an inhibitor, of cyclooxygenase, can inhibit human alveolar bone loss as measured radiographically.[10]

Role Of Host Response In Periodontal Disease –an Overview

It is now established & supported by enormous data that plaque biofilm and associated host response are involved in the pathogenesis of periodontal disease. The microbial challenge stimulates various host response mechanisms which result in destruction of the supporting periodontal structures. However, host response, being a double-edged sword, also has a protective side to it, which comprises of recruitment of neutrophils, production of protective antibodies, and the release of anti-inflammatory cytokines including Interleukin -1 receptor antagonist (IL-1ra), Tissue Inhibitors of matrix metalloproteinases (TIMPs), Interleukin-4 (IL-4), Interleukin-10 (IL-10) and Interleukin-11 (IL-11) (Page & Kornman 1997).[2] Perpetuation of the host response due to persistent bacterial challenge disrupts the homeostatic mechanisms and results in the recruitment of neutrophils and macrophages, and the release of mediators including pro-inflammatory cytokines (IL-6, IL-1), matrix metalloproteinases, arachidonic acid metabolites, reactive oxygen species, and mediators for osteoclastic bone resorption.[2]

Host cells are stimulated by constituents of the biofilm to produce pro-inflammatory cytokines including IL-1β, IL-6 and tumor necrosis factor-α (TNF-α), which may induce connective tissue and alveolar bone destruction.[11] Another hypothesis regarding periodontal disease pathogenesis is that the host cells stimulated directly or indirectly by components of the plaque biofilm, secrete the matrix metalloproteinases (MMPs). The matrix metalloproteinases are released by a variety of infiltrating cells[12] (i.e neutrophils and macrophages) and resident cells (i.e fibroblasts, epithelial cells, osteoblasts and osteoclasts) found in the periodontium. These matrix metalloproteinases are primarily responsible for connective tissue destruction.[13]

The components of immune inflammatory responses and their contribution to periodontal disease pathogenesis are discussed here under the following headings: arachidonic acid metabolites, matrix metalloproteinases, pro-inflammatory cytokines, production of nitric oxide, and regulation of bone remodelling.[14]

Role Of Host Response In Periodontal Disease : Arachidonic Acid Metabolites

The arachidonic acid metabolites include a variety of fatty acid-derived compounds that are enzymatically produced and released in response to local tissue injury. Arachidonic acid is a 20-carbon essential fatty acid (eicosanoid) which is normally present in mammalian cells in an esterified form within membrane phospholipids and is liberated from it by the action of phospholipase A2. Arachidonic acid serves as a precursor substrate for two enzymatic pathways : the Cyclooxygenase (COX) pathway and the Lipooxygenase (LO) pathway. The metabolism of Arachidonic Acid via the Cyclooxygenase pathway leads to the formation of the unstable cycloendoperoxide intermediates (PGG2 and PGH2), which ultimately results in the production of the Prostanoids (Prostaglandins, Thromboxane and Prostacyclin). The lipoxygenase pathway yields the hydroxyeicosatetraenoic acids (HETES) and the leukotrienes (LTs). In addition, a series of oxygenated arachidonic acid derivatives called lipoxins are formed by the interactions between the individual lipooxygenases (Los). This entire process is called the "*Arachidonic Acid Cascade*"[15]

A. Cyclooxygenase

Two isoforms of the enzyme COX have been identified and characterized.[9] Cyclooxygenase 1 is constitutively expressed and thought to maintain "housekeeping" functions (such as gastric cytoprotection and vascular and renal homeostasis). In contrast, cyclooxygenase 2 is inducible and thought to be involved in inflammation, cellular differentiation and mitogenesis.[70] In addition, COX-2 is upregulated by IL-1β, TNF-α, bacteria and lipopolysaccharide (LPS).[71] (Table – 1). Cells stimulated with cytokines such as IL-1β or LPS are able to rapidly synthesize COX-2 from pre-existing mRNA and translate new COX-2 transcripts, leading to a prolonged COX-2 release without inducing COX-1 biosynthesis. Cells stimulated with cytokines such as IL-1β or LPS are able to rapidly synthesize COX-2 from pre-existing mRNA and translate new COX-2 transcripts, leading to a prolonged COX-2 release without inducing COX-1 biosynthesis.[16]

Arachidonic Acid Metabolites As Mediators Of Bone Resorption

While studying mechanisms of bone resorption of mouse calvaria in tissue culture, **Goldhaber (1971)**[17] found that the resorptive process could be stimulated by prostaglandins produced by human gingival extracts or by prostaglandins secreted into the bone culture upon stimulation by an unidentified factor released from the gingival tissue. Almost contemporarily, **Klein & Raisz (1970)**[18] reported that prostaglandins and PGE2 specifically had the potential to induce bone resorption directly in organ culture. **Goodson et al. (1974)**[19] demonstrated with in vivo experiments that prostaglandins were implicated in the bone resorption process. A rapid bone resorption could be induced within 7 days after injection of a PGE1-containing solution under the skin of rat calvaria. In addition to prostaglandins, other AA metabolites such as Prostacyclin and Leukotriene appeared to be actively involved in bone resorption.

Prostacyclin (PGI2) is an endothelial cell product capable of preventing platelet aggregation and platelet adhesion to vessel walls. Findings from tissue culture experiments demonstrated that PGI2 stimulated bone resorption[18]. As cited by **Salvi and Lang (2005), Dewhirst (1984)**[18], in his experiments, observed that PGI2 rapidly and spontaneously hydrolysed to the inactive metabolite 6-keto PGF1α, which enzymatically oxidized to 6-keto PGE1α. This latter metabolite of PGI2, 6-keto PGE1α, stimulated significantly more bone resorption in tissue culture compared with 6-keto PGF1α, but its potency was about one-twelfth that of PGE2. On the other hand, the two main metabolites of PGI2 stimulated bone resorption with a similar potency **(Neuman & Raisz 1984)**[18] . Similarly, LTB4 has been shown to stimulate bone resorption in both in vitro and in animal models.[18]

Effect Of Prostaglandin E2 On Bone Metabolism And Periodontal Tissue Regeneration-

Prostaglandin E2 is a major product of cyclooxygenase-initiated arachidonic acid metabolism. Prostaglandin E2 has multiple and at times apparently opposing functional effects including fever, pain, vasodilatation, bone resorption, and formation, on a given target tissue and cell. The diverse effects of prostaglandin E2 are now explained by evidence for the existence of multiple prostaglandin E2 receptors (EP receptors) on plasma membranes. Pharmacological analysis and molecular cloning have revealed the existence of four EP receptor subtypes, each coded by distinct genes. These receptors are designated EP1, EP2, EP3, and EP4. The binding affinities of prostaglandin E2 to the EP receptors have the following rank order: EP3 > EP4 >> EP2 > EP1.[20]

It is very well known that cyclooxygenase-2 plays a crucial role in prostaglandin production in periodontal lesions.

DISCUSSION

The emergence of host response modulation as a treatment concept has resulted from our improved understanding of the pathogenesis of periodontal disease. Certain individuals appear to be more susceptible to periodontal disease, and this increased susceptibility is largely determined by the immune-inflammatory response that develops in the periodontal tissues following chronic exposure to bacterial plaque ,the microbial challenge presented by subgingival plaque results in an up-regulated host immune-inflammatory response in the periodontal tissues that is characterized by the excessive production of inflammatory cytokines (e.g.interleukins, tumor necrosis factor-a), prostanoids(e.g. prostaglandin E2) and enzymes [including the matrix metalloproteinases (MMPs). These pro-inflammatory mediators are responsible for the majority of periodontal breakdown that occurs , leading to the clinical signs and symptoms of disease.[21]

Periodontal disease is characterized by high concentrations of MMPs, cytokines and prostanoids in the periodontal tissues, whereas periodontal health is characterized by the opposite .Plaque bacteria therefore initiate the disease process, and bacterial antigens that cross the junctional epithelium into the underlying connective tissues drive the inflammatory response. Bacteria are therefore a necessary prerequisite for disease to develop but are insufficient to cause periodontal disease alone. For periodontal disease to develop, a susceptible host is also required, in other words a host in which excessive production of destructive enzymes (such as MMPs) and inflammatory mediators (e.g. interleukins and prostaglandins) are released during the cascade of destructive inflammatory events that occur as part of the inflammatory response . The purpose of host modulatory therapy is to restore balance between, on the one hand, pro-inflammatory mediators and destructive enzymes, and, on the other hand, anti-inflammatory mediators and enzyme inhibitors.21

Host modulatory therapy is a treatment concept that aims to reduce tissue destruction and stabilize the periodontium by down-regulating or modifying destructive aspects and/ or up-regulating protective or regenerative components of the host response. Host modulatory therapies could include systemically or locally delivered pharmaceuticals that are prescribed as adjuncts to other forms of periodontal treatment. Host modulatory therapies offer the opportunity to move periodontal treatment strategies to a new level. However, the outcomes after conventional treatment of this chronic disease are not always optimal, predictable or stable. Periodontal disease can be viewed as a balance between (i) a persisting bacterial burden and pro-inflammatory destructive events in the tissues, and (ii) resolution of inflammation and downregulation of destructive processes. Reducing the bacterial bioburden by root surface instrumentation targets one aspect of the pathogenic process by reducing the antigenic challenge that drives the inflammatory response in the tissues. However, complete elimination of all subgingival bacteria is not achievable , and recolonisation by putative pathogens occurs. Host response modulation therefore offers the potential for down-regulating destructive aspects of the host response in combination with conventional treatments to reduce the bacterial burden, so that the balance between health (characterized by resolution of inflammation and wound healing)and disease progression (characterized by continued pro-inflammatory, destructive events) is tipped in the direction of a healing response.[21]

Host response modulators offer the potential for modulating or reducing this destruction by ameliorating excessive or pathologically elevated inflammatory processes to enhance opportunities for wound healing and periodontal stability. A variety of drug classes have been evaluated as host response modulators, including nonsteroidal anti-inflammatory drugs, bisphosphonates, and tetracyclines . Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins, including prostaglandinE2, which is produced by a variety of resident and infiltrating cell types in the periodontium (including neutrophils, macrophages, fibroblasts and epithelial cells) in response to lipopolysaccharide. ProstaglandinE2 is a key inflammatory mediator in periodontal disease as it up-regulates osteoclastic bone resorption and prostaglandin E2 levels are significantly increased in the tissue and gingival crevicular fluid of patients with periodontal disease . Nonsteroidal anti-inflammatory drugs inhibit the formation of prostaglandins by blocking the cyclo-oxygenase pathway of arachidonicacid metabolism. They are used to reduce tissue inflammation and pain, and are indicated in a variety of chronic inflammatory diseases. The ability of nonsteroidal anti-inflammatory drugs to block prostaglandinE2 production, reduces inflammation and inhibits osteoclast activity.

Given the huge and ever-expanding range of pathogenic pathways that play a role in periodontal tissue destruction (for example, the interleukin-1 cytokine family is now far more complex than previously realized) it is invetible that the future will see a range of different host response modulators. Furthermore, most biological responses involve a range of different mechanisms, and therefore blocking one single inflammatory pathway may not achieve the desired outcome because receptor mediated responses could be activated by alternate pathways. Thus, polypharmaceutical approaches may be developed that modify a number of different pathways associated with inflammation and tissue destruction.21

Alternatively, targeting of mediators that play a particularly important role in periodontal pathogenesis, such as interleukin-1b or tumor necrosis factor-a, may constitute a rational therapeutic strategy. Thus, cytokine antagonists, such as interleukin-1 receptor antagonist or soluble tumor necrosis factor-a receptors, which competitively inhibit receptor-mediated signal transduction, may offer potential in the treatment of periodontal disease The effects of soluble receptors and receptor antagonists of interleukin-1 and tumor necrosis factor- a have been studied in experimental periodontitis, and collectively demonstrate a reduction in the progression of the inflammatory cell infiltrate towards the alveolar bone crest, reduced recruitment of osteoclasts, and decreased attachment loss and alveolar bone loss . Interleukin-11 has anti-inflammatory effects including inhibition of tumor necrosis factor-a, and recombinant human interleukin-11 has been shown to result in significant reductions in the rate of attachment and bone loss .Blockade of cytokine receptors, soluble cytokine blockers and anti-inflammatory cytokines therefore hold promise for the future. Other agents that block transcriptional pathways (e.g. the nuclear factor-kB and mitogenactivated protein kinase pathways), such as the protein kinase inhibitors, may be useful because genes that are regulated by nuclear factor-kB Vasoactive intestinal peptide has a role in immune-regulation and has been identified as a molecule with therapeutically beneficial immunosuppressive effects in inflammatory and autoimmune conditions. We have recently demonstrated that this immunologically active peptide significantly reduces tumor necrosis factor-a production in human monocytes stimulated with Porphyromonas gingivalis lipopolysaccharide and also inhibits nuclear translocation of nuclear factor-kB . expression of Toll-like receptor-2 and -4. It also blocks lipopolysaccharide-induced differentiation of monocytes to macrophages, possibly via inhibition of the transcription factor .However, it should be remembered that these pathways are important in physiological processes and therefore their inhibition could also result in adverse effects, such as increased susceptibility to infection. [21]

Lipoxins are another group of compounds that may ultimately be of benefit in modifying inflammatory responses in periodontal tissues. These lipid-derived mediators are released during inflammatory responses and have the effect of damping inflammation and modulating resolution of inflammation . Resolution of inflammation is now considered an active process, and failure of resolution of periodontal inflammation contributes to ongoing tissue breakdown. Lipoxins block interleukin-1b secretion from human neutrophils stimulated with tumor necrosis factor and block neutrophil migration following exposure to P. gingivalis. In an experimental periodontitis study of transgenic rabbits overexpressing 15-lipoxygenase and in nontransgenic animals receiving topical application of 15-epi-lipoxin A4, enhanced expression of 15-lipoxygenase as well as topical 15- epi-lipoxin A4 significantly reduced bone loss and gingival inflammation . These results suggest that, lipoxins can be targets for novel approaches in diseases such as periodontitis in which inflammation and bone destruction occur. [21]

Summary And Conclusion

Periodontal disease is a multifactorial and complex disease which is primarily caused by the noxious products produced by the bacteria and the inflammatory products produced by the host in response to the bacterial stimuli.

Bacterial biofilms have been shown to be the primary etiological factor

in the initiation of gingival inflammation and subsequent destruction of periodontal tissues. At the same time there is strong evidence that destructive processes occurring as part of the host inflammatory response are responsible for the majority of the hard and soft tissue breakdown leading to the clinical signs of periodontitis. The precise nature of the host inflammatory response is still an area of intense research, but it is clear that host-derived pro-inflammatory mediators and cytokines, together with proteolytic enzymes such as matrix metalloproteinases (MMPs), play a significant role for causing changes in connective tissue and bone metabolism that lead to the breakdown of periodontal ligament (PDL) and alveolar bone resorption. Therefore, the successful long-term management of this disease may require a treatment strategy by integrate therapies that will address both causative components.

To date, non-surgical periodontal treatment has primarily focused on targeting the bacterial burden by mechanical disruption of the subgingival biofilm by SRP or by locally delivered antimicrobial agents with SRP to further reduce the bacterial burden. It is clear that standard therapy, such as the removal of supragingival and subgingival plaque and calculus, by scaling and root planing has been found to be effective for the majority of the patients associated with periodontitis. However, there is strong evidence that in some patients destructive processes occurring as part of the host inflammatory response are responsible for the periodontal tissue breakdown leading to the clinical signs of periodontitis.

Therefore, adjunctive use of therapeutic agents which modify the destructive nature of the host response to periodontopathogens are potentially valuable to the clinical treatment of periodontitis.

Studies ranging from preclinical animal models to human clinical trials support the basic hypothesis that the inhibition of local arachidonic acid metabolites with nonsteroidal anti-inflammatory drugs (NSAIDs) prevents periodontal disease progression. However, recently reported serious adverse effects of some COX-2 inhibitors preclude their use as an adjunct to mechanical periodontal therapy. Tetracyclines and doxycycline in particular are known to inhibit MMP activities either by direct or indirect non-antimicrobial mechanism, thus preventing connective tissue breakdown and bone resorption. Evidence shows that non-surgical periodontal therapy with an adjunctive use of 20 mg SDD twice daily for 9 months was shown to down-regulate collagenolytic activity and thereby improvement in clinical response. Recently bisphosphonate therapy has been tried to prevent periodontal disease progression due to its ability to inhibit osteoclast recruitment and down-regulate levels of several MMPs. However, controversial data on the effects of systemic bisphosphonate administration to prevent periodontal disease progression have been reported both in animal experiments and human studies.

In addition to these extensively studied groups of drugs newer therapeutic approaches have also been tried. Most of these approaches are still in the infancy and limited to animal experimental studies only. Investigations on use of soluble protein delivery of antagonists to interleukin-1 and tumor necrosis factor in a primate model of periodontitis have shown promising results by blocking progression of inflammatory cell infiltrate towards the alveolar crest, thereby preventing periodontal attachment loss. Similarly, the use of, a pharmacological inhibitor of NO and POLY(ADP-RIBOSE) POLYMERASE (PARP) synthatase showed promising result in reducing periodontal attachment loss. Recently, it has been suggested that diagnosis of active bone loss by measuring the ratio of receptor activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) may prove to be a novel diagnostic parameter. However, further studies are necessary to determine the applicability of these agents as therapeutic drugs. It is conceived that new potential agents to modulate host response may be developed in future.The treatment of periodontal disease should also focuses on eliminating all the local etiological factor , that focuses on the reduction of bacterial count .However , this conventional approach of elimination of infectious agents may not always provide the assurance of a definitive treatment of periodontitis.

Thus host modulation therapy is designed to inhibit various pathways which are responsible for periodontal disease these pathways include arachidonic acid meatbolites, matrixmetalloproteinases, proinflammatory cytokines production of nitric oxide and regulation bone remodelling.

To summarize, host response modulators must be viewed as comprising part of the overall management strategy for patients with periodontitis. Thus, they should form part of an integrated treatment approach, together with oral hygiene maintenance, plaque control, root surface instrumentation, maintenance care and risk factor modification. Periodontal disease is an unfortunate and distressing condition, and many patients are relieved to realize that multifaceted treatment strategies are possible, including, for example, root surface instrumentation, enzyme suppression and modification of local and systemic risk factors. Thus, periodontal therapy in the 21st century should not only involve a high standard of clinical treatment and monitoring, but should also focus on patient involvement and improving the patient experience. The future will see a range of host response modulators developed as adjunctive treatments for periodontitis. At present, subantimicrobial dose doxycycline provides improvements in probing depth reductions and attachment gains compared with root surface instrumentation alone. Although the use of nonsteroidal anti-inflammatory drugs has been associated with reduced alveolar bone loss, the unwanted effects of these drugs precludes their use. Similarly, although data supporting the use of bisphosphonates to improve clinical periodontal status have been published, given the association with osteonecrosis, further studies are warranted to determine the risks and benefits of these drugs. Lipoxins and compounds that block cytokine receptors have been shown to reduce gingival inflammation and bone loss and may represent the future of host response modulation for treating periodontal disease, although this remains to be demonstrated in clinical trials in humans.
Thus , increased application of host modulation therapy in periodontal disease management should be explored to effectively control and prevent the periodontal disease progression .

REFERENCES

1. Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol 2008; 79:1585-1591.
2. Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. Periodontol 2000 1997;14:9-11.
3. Kantarci A, Van Dyke TE. Lipoxins in chronic inflammation. Crit Rev Oral Biol Med 2003; 14 (1):4-12.
4. Ryan ME. Connective Tissues of periodontium; research & clinical ramifications. Perio 2000, Vol 24;2000: 227-234.
5. Kirkwood KL, Cirelli JA, Rogers JE and Giannobile WV. Novel Host Response Therapeutic Approaches to treat periodontal diseases in Periodontol 2000. Vol 43; 2007; 294-315.
6. Giannobile WV. Host-Response Therapeutics for Periodontal Diseases. J.Periodontol 2008; 79:1592-1600.
7. Thomas Van DYKE .Management of inflammation in periodontal diseases.J.Periodontol 2008;79:1601-1608
8. Heasman, P. A., Offenbacher, S., Collins, J. G., Edwards, G. & Seymour, R. A. Flurbiprofen in the prevention and treatment of experimental gingivitis. J Clin Periodontol 1993b; 20:732–738.
9. Offenbacher S. Periodontal Diseases: Pathogenesis. Ann Periodontol 1996; 1: 821 – 878.
10. Offenbacher S, Peter A. Heasman, and John G. Collins Modulation of Host PGE2 Secretion as a Determinant of Periodontal Disease Expression. J Periodontol 1993; 64:432-444.
11. Berdeli A, Gurkan A, Emingil G, Atilla G, and Kose T. Endothelial Nitric Oxide Synthase Glu298Asp Gene Polymorphism in Periodontal Diseases in J Periodontol 2006; 77: 1348-1354.
12. Gullu C, Ozmeric N, Tokman B, Elgun S, Balos K. Effectiveness Of Scaling And Root Planing Versus modified Widman flap on Nitric Oxide Synthase And Arginase Activity In Patients With Chronic Periodontitis in J Periodont Res 2005; 40: 168-175.
13. McCauley LK and Nohutcu RM. Mediators of Periodontal Osseous Destruction and Remodeling: Principles and Implications for Diagnosis and Therapy. J Periodontol 2002; 73: 1377-1391
14. Morton, R. S. & Dongari-Bagtzoglou, A.I. Cyclooxygenase-2 is upregulated in inflamed gingival tissues. J Periodontol 2001; 72, 461–469
15. Salvi GE, Lang NP. Host response modulation in the management of periodontal diseases in J Clin Peridontol 2005; 32 (Suppl. 6): 108–129.
16. Francisco Mesa, Mariana Aguilar. COX-2 expression in gingival biopsies from periodontal patients is correlated with connective tissue loss. JOP 2012; 83: 1538-1545
17. Goldhaber, P. (1971) Tissue culture studies of bone as a model system for periodontal research. Journal of Dental Research 50, 278–287.
18. Goodson, J. M., Mc Clatchy, K. & Revell, C. (1974) Prostaglandin induced resorption of the adult rat calvarium. Journal of Dental Research 53, 670–677.
19. Drisko C.H. Non-Surgical Pocket Therapy: Pharmacotherapeutics in Annals Periodontol 1996; 1: 491 – 566.
20. Miyauchi M, Ijuhin N, Nikai H, Takata T, Ito H, Ogawa I. Effect of exogenously applied prostaglandin E2 on alveolar bone loss-histometric analysis. J Periodontol 1992: 63: 405–411.
21. Kazuyuki Noguchi & Isao Ishikawa. The roles of cyclooxygenase-2 and prostaglandin E2 in periodontal disease. Periodontology 2000, Vol. 43, 2007, 85–101.