HOST MODULATION THERAPY: AN UPDATE

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Abstract:
Through the alteration of host response variables, inflammatory tissue can be stabilised or even grown again through the use of a therapeutic approach known as host modulation therapy (HMT). Host modulation agents that are administered locally or systemically as part of periodontal therapy. They are used as supplements to more traditional periodontal therapies including surgery and scaling and root planing. This article aims to provide an overview of the existing literature on HMT and its application as a complementary therapy in periodontics.

DOI Number: 10.48047/nq.2022.20.9.nq44877 **NeuroQuantology 2022;20(9):7513-7520**

Introduction: The goal of host modulation therapy (HMT) is to alter or down-regulate the destructive parts of the host response and up-regulate the protective or regenerative responses in order to minimise tissue damage and stabilise or even regenerate the periodontium. Simply said, in the context of periodontics, it refers to adjusting or regulating elements of the inflammatory host response that cause damage or destruction to emerge in the periodontal tissues as a result of the ongoing challenge posed by the subgingival bacterial plaque.[1]Periodontitis is multifactorial infectious disease of the supporting structures of the teeth, characterized by destruction of the bone and connective tissue. Specific periodontopathic bacteria and their virulence factors are the primary etiologic agents.[2] HMT provides opportunities to both upregulate the protective (inflammatory resolution) and downregulate the destructive (proliferating proinflammatory events) components of the host response.[3]

Rationale of Host modulation therapy

- By supplementing the natural inherent defense mechanism, It helps the host combat pathogenic infections and the byproducts they produce.
- HMT has the ability to both upregulate the protective (inflammatory resolution) and downregulate the damaging (proliferating proinflammatory events) components of the host response.

Pathogenesis of periodontal disease for modulation[3]

The following HMT techniques have been developed to either block or alter the pathways associated with periodontitis:

- Inhibition of arachidonic acid metabolite
- Inhibition of matrix metalloproteinase (MMPs)
- Modulation of bone metabolism
- Regulation of immune and inflammatory response

Inhibition of arachidonic acid metabolite

The production and release of prostaglandins and other metabolites of arachidonic acid (AA or ARA) inside periodontal tissues is one of the routes implicated in the development of periodontal disease.

Either the lipoxygenase (LO) or cyclooxygenase (CO) pathways can be used to metabolise AA.

Prostaglandin E2, which is generated by a number of resident and invading cell types in the periodontium in response to lipopolysaccharide, is one of the prostaglandins that nonsteroidal anti-inflammatory medications block. A number of NSAIDs, including indomethacin, flurbiprofen, naproxen, sulindac, meloxicam, ketoprofen, and ibuprofen, are being studied for their potential to treat HMT.[5]

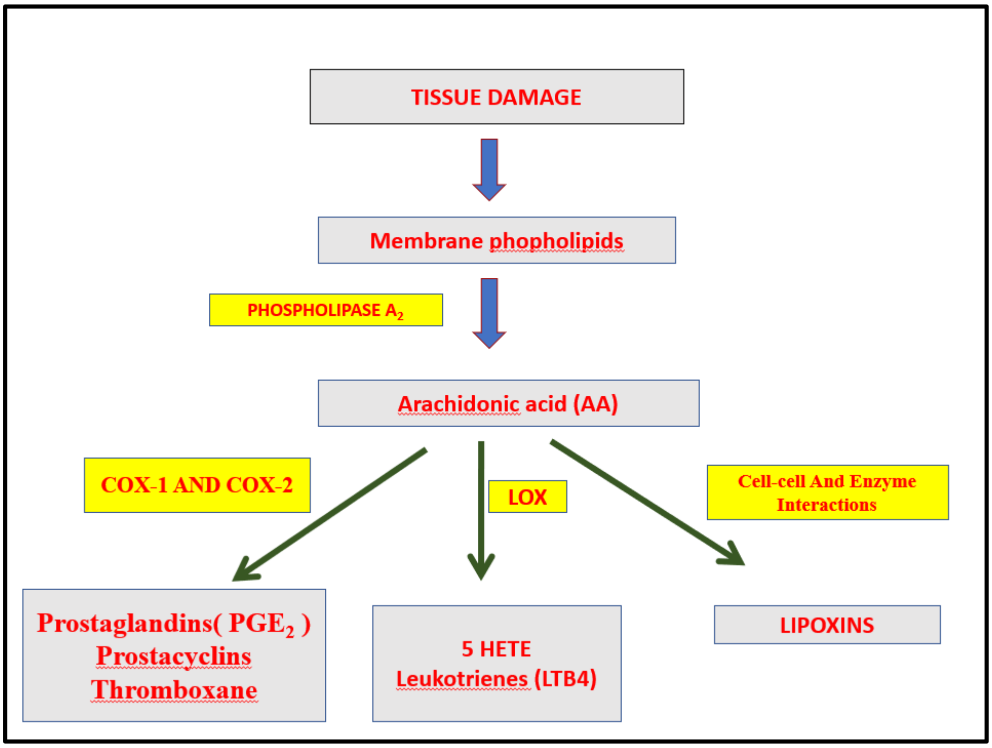

Figure1: Inhibition of arachidonic acid metabolite through NSAIDS

Anti- proteinase blocking of matrix metalloproteinases (MMP's)

Matrix Metallo Proteinases (MMPs) are a class of calcium-requiring and zinc-dependent endopeptidases that are essential to numerous biological processes, including angiogenesis, normal tissue remodelling, embryogenesis, wound healing, and diseases like tissue ulceration, arthritis, and cancer.[5]

An imbalance of matrix metalloproteinases over tissue inhibitors of metalloproteinases is frequently linked to tissue degradation in disease processes. Tissue inhibitors of metalloproteinases (TIMPs) are significant regulatory factors in the activities of matrix metalloproteinases.They are of two types:[5]

1. TIMPs and α-2 Macroglobulin are Endogenous inhibitors - MMP activities are likely pericellularly regulated by TIMPs, while α2-macroglobulin operates in bodily fluids. However, α2-macroglobulin acts in the extracellular matrix and exits the vascular during inflammation.
2. Exogenous: (synthetic inhibitors) - Exogenous inhibitors include zinc and calcium chelating agents, phosphorous containing peptides, sulfur-based inhibitors, hydroxamic acid inhibitors.

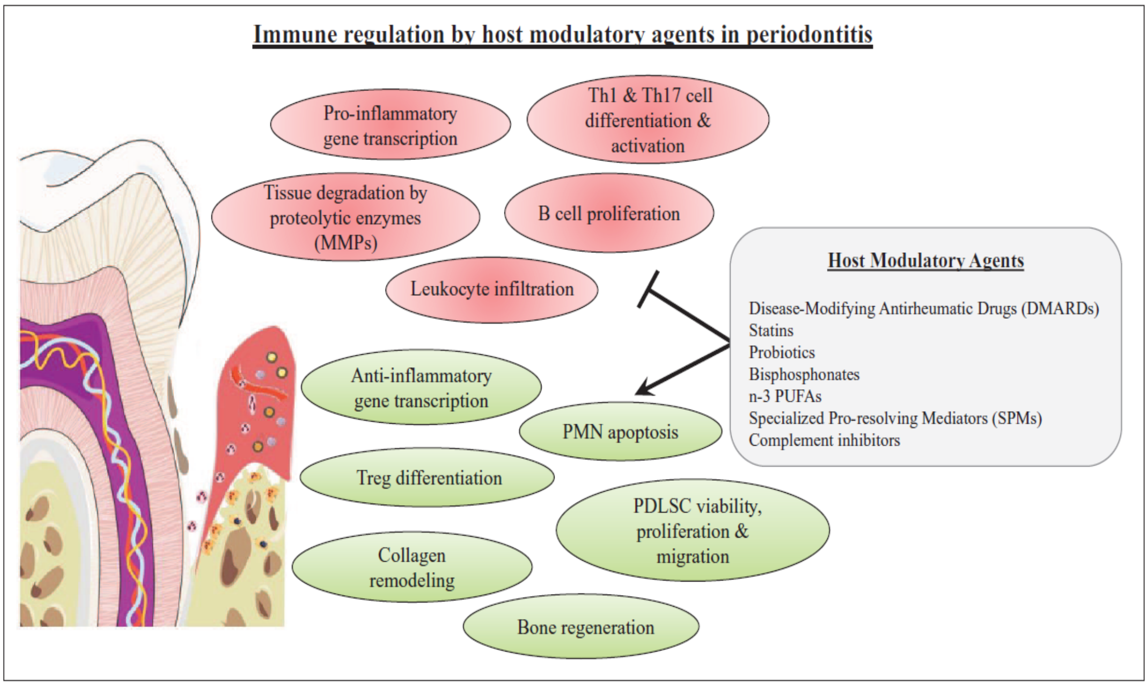

Figure 2: Immune regulation by host modulatory agents in periodontitis[6]

Regulation of immune and inflammatory response

ANTI-CYTOKINE THERAPY

Cytokines are classified as regulatory proteins that govern the viability, proliferation, differentiation, and operations of cells. Cytokines act and are broken down in a local context, and they are created transiently at typically low quantities. Cytokine-producing cells are frequently found physically next to responsive cells, which serves as evidence for this. Many biological reactions can be mediated by many cytokines, however relatively few responses are mediated by a single cytokine.[3]

Down regulation of cytokines is mainly brought about by three mechanisms[7]

i. cytokine receptor antagonist: Cytokine receptor antagonists bind to the receptor present on the target cell and prevent the cytokine from binding to the target cell. Therefore, there is no activation of the target cell.

ii. Soluble cytokine receptors: Soluble cytokine receptors are derived from the proteolytic cleavage of the extracellular domain of cell-bound cytokine receptors. Soluble receptors can be found in blood and extracellular fluid.

They cause:

1. Downregulation: The cytokine in solution is bound by soluble receptors, which stop signalling.

2. Transactivation: On cells that would not normally respond, soluble receptors bind to cytokines and dock to activate them. Only sIL-6R, among these soluble receptors (sTNF-RI, sTNF-RII, sIL-1R, and sIL-6R), functions as an agonist; the other soluble receptors all serve as antagonists and cause the downregulation of cytokines.

3. Anti-cytokine antibodies: these antibodies also have an antagonistic effect and reduce cytokine levels. (Anti-TNF-Ab, Anti-IL-6 Ab)

Modulation of bone metabolism

Inhibitors to RANK/RANKL Interaction[8]

A ligand for osteoprotegerin, " Receptor Activator of NF-κB Ligand” RANKL is a member of the tumour necrosis factor (TNF) cytokine family and plays a crucial role in osteoclast activation and differentiation. In the immune system, T helper cells produce RANKL, which is believed to have a role in the development of dendritic cells. It has been demonstrated that this protein contributes to the survival of dendritic cells and controls the T cell-dependent immunological response. The following substances increase the expression of the RANKL gene in osteoblasts/stromal cells: vitamin D3, PTH, IL-1, IL-6, IL-17, TNF-α, BMP-2, and PGE2.

Host Modulatory Agents[9]

Various host modulatory therapy agents have been developed to prevent and management for the periodontal disease. The most common mechanisms by which these acts are the following:

1. Inhibition of Matrix metalloproteinases (MMPs) -Through chemically Modified Tetracyclines (CMTs)

2. Inhibition of Arachidonic Acid metabolites- through NASIDs

1.COX-1 inhibitors: Indomethacin's, Flurbiprofen

2.COX-2 inhibitors: Rofecoxib

3.COX and LOX inhibitors: Triclosan, Tropical Ketoprofen

4.LOX inhibitors: Lipoxins

3. Modulation of Bone metabolism

1.Bisphosphonates

2. Hormone Replacement Therapy

4. Regulation of immune and inflammatory responses

1.Suppressing proinflammatory cytokines (IL-1 and TNF- α receptor antagonists)

2.Nitric Oxide inhibition

3.Generation of protective antibodies through vaccine

4.Infusion/ supplementary anti-inflammatory cytokines IL-4 and IL-10.

5. Miscellaneous Host Modulatory agents

1.Aloe vera

2.Probiotics

3.Hypochlorous acid and taurine-N-monochloramine

4.Azithromycin's

A. Chemically Modified Tetracyclines (CMTs)[10]

For a very long period, tetracyclines have been employed as antibiotics. MMPs are produced by periodontal pathogens, specifically P. gingivalis and A. actinomycetemcomitans. That being said, it is thought that bacterial proteinases rather than endogenous MMPs are the main cause of tissue damage. This emphasises even more how crucial host modulatory techniques are to periodontal treatment. Tetracyclines that have had their fourth carbon atom's dimethylamino group removed are known as chemically modified tetracyclines.

Mechanism of Action of Chemically modified tetracyclines

1. Prevents or chelates the calcium atoms necessary for the function of matrix metalloproteins.
2. Blocks MMPs that are already activated.
3. Reduces the expression of MMPs
4. Reactive oxygen species scavengers
5. Alters the functioning of osteoclasts

Side effects of CMTs

1. Property of photosensation
2. Toxicology to the nervous system
3. Effects of cytotoxicity at elevated concentrations.
4. Bacterial resistance.

Periostat (Subantimicrobial dose of doxycycline)

This 20 mg doxycycline hyclate capsule employs tetracycline's anticollagenase capabilities as a subantimicrobial dosage. For individuals with persistent periodontitis, it is recommended twice a day. medicine is administered for an only two weeks. In individuals with chronic periodontitis, this can reduce collagen activity in the gingival tissue by 60% to 80%. But in GCF, collagen activity also declines. Medication resistance is less likely when prescribed for a shorter period of time. When treating periodontal disorders, it is a useful supplementary technique to mechanical treatment.[11]

Mechanism of Action

By directly suppressing MMPs, which are released by plaque biofilm, it functions as a host modulator, indirectly lowering osteoclast activity and bone resorption. It increases bone absorption by boosting osteoblast activity. It also encourages the fibroblasts to produce collagen.

Indications

1. Individuals who have not improved with non-surgical treatment.
2. Individuals whose pockets are 5 mm or deeper and exhibit widespread recurring spots that bleed when prodded.
3. Individuals with mild to severe chronic periodontitis who are more susceptible to the fast advancement of periodontal disease.
4. A patient suffering from Aggressive periodontitis
5. A particular difference in the genes that control IL-1 is present in patients with periodontitis associated with genotype (PAG).

Contraindications[9]

1. The patient with tetracycline allergy.
2. Women who are expecting, nursing, and kids under the age of twelve.
3. The patient who requires an antibiotic therapy.
4. May decrease oral contraceptive efficacy.

B. NSAIDS (Non-Steroidal Anti-inflammatory Drugs)

Inhibition of Arachidonic Acid metabolites[12]

Destructive pathways are triggered in periodontal diseases by the activation of arachidonic acid, which is then metabolised by cyclooxygenase and releases prostaglandins, prostacyclins, and thromboxane. Meanwhile, the lipoxygenase pathway ultimately releases hydroxy eicosatetraenoic acid and leukotrienes. Therefore, inhibiting the enzymes that cause the production of these harmful chemicals is one way to modify the host response. Among them are:

1. Systemically administered NSAIDS
2. Locally administered NSAIDS
3. Triclosan

Systemically administered NSAIDS

Nonsteroidal anti-inflammatory medications work by blocking the arachidonic acid pathway's cyclooxygenase. lowering prostaglandins (PGE2), which are in charge of bone resorption. These consist of indomethacin and ibuprofen.[13]

Locally administered NSAIDS

Another way to administer these medicines is topically. Because these medications are lipophilic and absorb into gingival tissues, it is conceivable. Among these is ketoprofen, which blocks the lipoxygenase and cyclooxygenase pathways. In addition, S-ketoprofen dentifrices and ketorolac trimethamine rinse can be utilised.[14]

Triclosan

Its anti-inflammatory and antibacterial qualities are combined. In addition to inhibiting the cyclooxygenase and lipoxygenase pathways, this non-ionic antibacterial antibiotic also interferes with the arachidonic acid route.[15]

C. Bisphosphonates[16]

Drugs known as bisphosphonates are non-biodegradable pyrophosphate analogues that have a strong affinity for calcium phosphate crystals and suppress osteoclast activity. These bisphosphonates seem to work by chelating cations in order to suppress MMP activity.

Mechanism of Action

1. Prevention of osteoclast formation
2. Osteoclastic apoptosis induction
3. Decrease in osteoclast activity
4. Preventing hematopoietic cells from becoming osteoclasts
5. Starts the synthesis of an inhibitory factor for osteoclasts.
6. Induce osteoclast inhibitory factor synthesis.
7. Reducing bone mass by blocking MMPs.

Disadvantages

1. Prolonged usage can hinder the healing of even small bone damage.
2. May cause the jaw to develop osteonecrosis after tooth extraction.
3. Prevent the calcification of bone.

Bisphosphonate Modulation of bone metabolism		
Tissue Level	**Cellular Level**	**Molecular Level**
• ↓sed Bone turnover due to ↓sed Bone resorption. • ↓sed Number of new bone multicellular units. • Net positive whole body bone balance.	• ↓sed Osteoclast recruitment • ↑sed Osteoclast apoptosis • ↓sed Osteoclast adhesion • ↓sed Depth of resorptionsite • ↓sed release of cytokines by macrophages. • ↑sed Osteoblast differentiation and number.	• Inhibit mevalonate pathway (that result in perturbed cell activity and induction of apoptosis). • ↓sed Post-translational prenylation of GTP-bonding proteins.

Table 3: Bisphosphonate Modulation of bone metabolism

D. Osteoprotegerin (OPG)[9]

Osteoprotegerin, a novel receptor, was shown to be a critical regulator of osteoclast differentiation and activity. Osteoclast production and bone resorption are regulated by two molecules: OPG and receptor activator of NF-kappa B (RANKL) ligand. Osteoclasts are affected by RANKL because it causes osteoclast development and activation, while OPG prevents this action by functioning as a RANKL decoy receptor.

E. Statins[17]

These medications are used to treat hyperlipidemia because they decrease the body's lipid levels. These medications have pleiotropic properties that include vasodilation, antioxidant, antithrombotic, and anti-inflammatory actions. They prevent the 3-hydroxy-3-methyl glutaryl coenzyme from functioning.

Mechanism of Action

Via preventing the release of proinflammatory mediators such as cytokines and MMP and this inhibit osteoclast activity.

F. Regulation of immune and inflammatory responses

1. Modulation of Nitric Oxide activity: The chemical nitric oxide (NO) is involved in many different biological activities. It is a very reactive free radical that reacts with metal and thiol residues to cause cytokine release, protein degradation, lipid peroxidation, and DNA damage. NO toxicity is reduced by the nuclear poly ADP-ribose polymerase enzyme.[18]

2. Suppressing proinflammatory cytokines: Regulation proteins that govern the viability, proliferation, differentiation, and functions of cells are known as cytokines. They share overlapping properties, are generated by several cell types, and operate as a network. Biological redundancy is the term for this occurrence. Cytokines antagonists that competitively block receptor-mediated signal transduction, such as soluble TNF receptors or IL-1 receptor antagonists, can prevent tissue damage and preserve homeostasis.[19]

3. Other Locally administered agents: These include substances that have been studied for possible use as surgical procedure adjuncts, including as growth factors, enamel matrix proteins, and bone morphogenic proteins. It restores the entire periodontal attachment system by promoting the regeneration of missing bone, cementum, and periodontal ligament in addition to improving wound healing.

Enamel matrix protein

Emdogain is the only local host modulatory medication that is now FDA-approved for use as an adjuvant during surgery. Early phases of osteoblast maturation are affected by it. They are thought to control the beginning, spreading, ending, and maturation of hydroxyapatite crystals in enamel. They participate in cementogenesis as well.[9]

Hertwig's epithelial root sheaths are thought to produce enamel-related matrix proteins during a secretory phase during the formation of the root and attachment apparatus. commercially accessible and FDA-approved AS Emdogain® (Biora AB, Malmö, Sweden). The basic idea behind utilising Emdogain is that it will function as a tissue-healing modulator, helping to accelerate periodontal regeneration by mimicking the activities that take place during root growth. It initiates periodontal regeneration through recruitment of cementoblasts to the root-surface and stimulates these to form root-cementum, which will thereafter secondarily lead to regeneration of periodontal fibers and alveolar bone.

Bone morphogenetic protein (BMP)[9]

BMP directs mesenchymal cells' regulation and differentiation into bone and bone marrow cells. Under the brands INFUSE® Bone Graft (Medtronic, Minneapolis, MN, USA) and InductOSTM (Wyeth, Maidenhead, UK), absorbable collagen sponge (ACS) containing recombinant human BMP-2 has been authorised for clinical usage in specific oral surgical procedures, including localised alveolar ridge augmentation. These ACS act as a framework for the growth of new bone, releasing the protein over time at the implanted site. The allograft site heals, allowing bone to grow in its place and absorb the ACS.

Platelet derived growth factor[9]

Growth-factor Enhanced Matrix, GEM 21S® (Osteohealth, Shirley, NY) is now authorised by the FDA. It combines an osteoconductive bone matrix with a highly pure, bioactive human recombinant PDGF-BB. It boosts the chemotaxis of monocytes and neutrophils, promotes the fibroblasts' proliferation and the synthesis of extracellular matrix, boosts the proliferation and differentiation of endothelial cells, and promotes the mesenchymal progenitor cells' and fibroblasts' differentiation.

Conclusion: Although several clinical trials have proven the effectiveness and utility of host modifying medicines, and the FDA has authorised these medications for the treatment of periodontitis, the risk/benefit ratio associated with their usage is still unknown. Comprehensive assessments of the advantages of these drugs and a comparison of their utility and long-term administration hazards necessitate multicenter clinical studies. Ongoing studies in this area might also make it possible to develop customised treatments for periodontal disease that target the inflammatory host response.

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