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Host Modulation Therapy in Periodontology: An In-Depth Review and Future Perspectives

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Abstract: ***Host modulation therapy is a concept that decreases the periodontal tissue destruction that is result of host response. HMT decrease destruction stabilizes and also regenerates the tissue by modulation of host response. Severe periodontal destruction has seen in many patients and most of which is due to hosts own response to the initial bacteria or foreign agents. Thus, use of HMT is reported to very beneficial in these cases, but in recent times also use of HMT and is awareness is very less. This article aims to reintroduce HMT with all its advantages and disadvantages. Various researches along with their results are also added here to further stress on the fact that HMT in addition to conventional scaling root planning is the need of modern medicine.***

Keywords: Host modulation, NSAIDs, Matrix Metalloproteinase, Pro-I Cytokines

1. Introduction

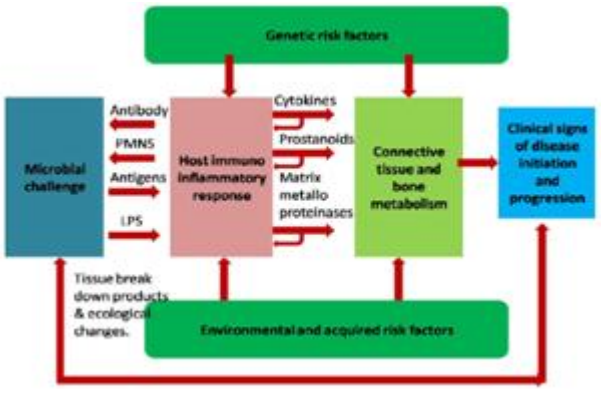
Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both."[1]

As many as 600 different species of bacteria that colonize the oral cavity can affect the delicate balance of host-bacterial interactions leading to health or disease. This chronic challenge of virulent microorganisms leads to destruction of tooth-supporting soft and hard tissues of the periodontium. Although periodontitis is initiated by the subgingival microbiota, it is generally accepted that mediators of connective tissue breakdown are generated to a large extent by the host′s response to the pathogenic infection[1]. So, controlling the host response and decreasing the degrading effect of this can lead to very effective periodontal therapy.

Host modulation if broken to its constituents i. e HOST meaning an organism that is infected with or is fed upon by a parasitic or pathogenic organism and MODULATION means the ability to control, influence or change a particular physical process. Certain putative periodontal pathogens predominantly Gram-negative, anaerobic bacteria within biofilm are associated with periodontal disease initiation and progression. The microbial challenge consisting of antigens, lipopolysaccharide and destruction is primarily by the host responses. The host responses are of mainly two types: anti-inflammatory or protective and proinflammatory or destructive[2]. Pro-inflammatory cytokines initiate inflammation stimulate osteoclast to proliferate and differentiate, they induce production of PGE2 that is responsible for induction of MMPs so they play a key role in periodontitis. Since the destruction of periodontal tissue is caused by the host response; modulation of host response which aims to stop periodontal tissue destruction, stabilize or even regenerate is a promising approach to improve the therapeutic outcome of periodontal disease. Once pro-inflammatory cytokines are controlled, MMPs, prostaglandins and osteoclasts will be controlled. This may be accomplished by different ways such as down regulation of pro-inflammatory cytokines, up regulation of anti-inflammatory cytokines. Other aspects of host modulation include protein kinase inhibitors, arachidonic acid metabolites; bone remodeling, nitric oxide synthase inhibitors and antioxidants[3].

HMT aims to decrease tissue destruction and normalize the periodontium by down regulating destructive agents of the host response and up regulating protective processes. These pharmaceuticals are prescribed as part of periodontal therapy and used as adjuncts to conventional periodontal therapy. This article aims at explaining importance of HMT and to review the fact that HMT therapy in addition of scaling and root planning can give better results than conventional periodontal therapy.

2. Pathogenesis of Periodontal Disease



Periodontal disease pathogenesis is associated with parasite-host interactions that are elicited predominantly by plaque biofilm endotoxins, lipopolysaccharide (LPS), a major component of the outer cell membrane of Gram negative bacteria, initiating a cascade of events[4]. LPS and other virulence factors stimulate host immune and inflammatory responses which initially results in disease limited to gingiva or initiation of periodontal destruction due to persistent microbial challenge. Protective host response includes recruitment of neutrophils, production of protective antibodies and release of anti-inflammatory cytokines including transforming growth factor-β (TGF-β), interleukin (IL)-4, IL-10, IL-11 and IL-12. The destructive host response includes release of pro-inflammatory mediators; cytokines (e.g. IL-1, IL-6, Tumor Necrosis Factor-α [TNFα]), proteases (e.g. matrix metalloproteinase) and prostanoids (e.g. prostaglandin E2 [PGE2]). Homeostasis is essential in between pro-inflammatory and anti-inflammatory mediators, disruption of which results in extra-cellular matrix destruction and bone resorption and the resultant clinical manifestation as a periodontal disease.[5, 6] Various environmental, acquired or genetic risk factors e.g. smoking, diabetes mellitus that cause excessive host response or hyper inflammation will lead to increased periodontal tissue damage[2].

Classification of HMT

Systemically administrated agents:

- SDD (Sub-antimicrobial dose of doxycycline)
- NSAIDS (Non-steroidal anti-inflammatory drugs)
- Bisphosphonates
- Modulation of NO (Nitrous oxide) activity

Locally administrated agents

- NSAIDS
- Enamel Matrix Protein
- Growth Factor

Host Modulatory Agents

Various Host modulatory agents that have been developed to down regulate the host responses are as follows:

- Inhibition of matrix metallo-proteinases (MMPs)-through CMTS
- Inhibition of arachidonic acid (AA) metabolites – through NSAIDS
- Modulation of bone metabolism
- Regulation of immune and inflammatory responses
- Miscellaneous

1) Inhibition of Matrix Metalloproteinase

MMPs lead to remodeling of the extracellular matrix, including collagen and proteoglycans. MMP-8 and MMP-9 are the predominant MMPs produced by neutrophils and degrade type I collagen. Chemically-modified tetracycline usually lack dimethyl amino group on the 4th carbon atom are used to inhibit these MMP`s.

Mechanisms of action of CMT's:

- Inhibits or chelates the calcium atoms and subsequently hinders the action of MMPs due to lack of calcium.
- Inhibits already active MMP's.
- Down regulates MMP's expression.
- Acts as reactive oxygen species (ROS) scavengers.
- Modulates the osteoclast functions

Sub- antimicrobial-dose doxycycline (SDD)

Only host modulation therapy accepted by the U. S. Food and Drug Administration is Periostat. SDD (Periostat) is usually administered in very small doses for approximately 3 months. Administration of SDD must be done for minimum 3 months to avoid any reoccurrence and it is often prescribe for a span of 9 months also with regular follow ups. This minimal dosage of SDD is below the detection of bacteria so it avoids any resistance. So, this makes SDD a better option than other HMTs.

2) Inhibition of Arachidonic Acid Metabolism: through NSAID'S

Periodontal disease leads to initiation of a series of events which eventually leads to secretion of prostaglandins. Prostaglandins lead to the increased destruction causing more damage than elicited by bacteria. Prostaglandin is the result of metabolism of arachidonic acid. Arachidonic acid is metabolized by cyclooxygenase (COX) or lipoxygenase (LOX) pathways, so inhibition of the same is key to solving the problem.

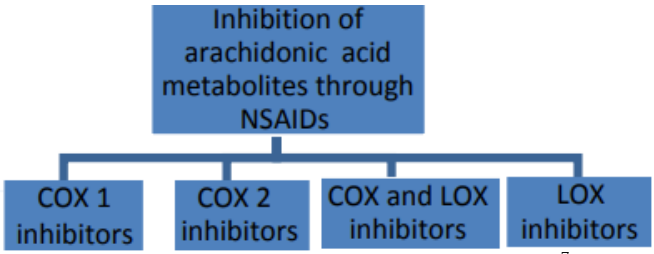


Figure: Inhibition of arachidonic metabolites[7]

Non-steroidal anti-inflammatory drugs-NSAID's lead to down regulate production of prostaglandins. Elevated prostagladins are normally seen in cases of periodontitis. Prostagladins are responsible for bone loss. Use of NSAID's is done due to their ability to block COX pathway which inhibits prostagladins secretion and control bone loss. Prolonge use of NSAID's as host modulation therapy can cause some side effects like gastrointestinal pain and ulcer, bleeding, and renal impairment and also some rebound effects has been seen when administration of NSAID's was stopped which is why these are not yet accepted as host modulation therapy for periodontitis. Various researches have been going on NSAID's for HMT on drugs like, ibuprofen, naproxen, meloxicam, ketoprofen and sulindac.

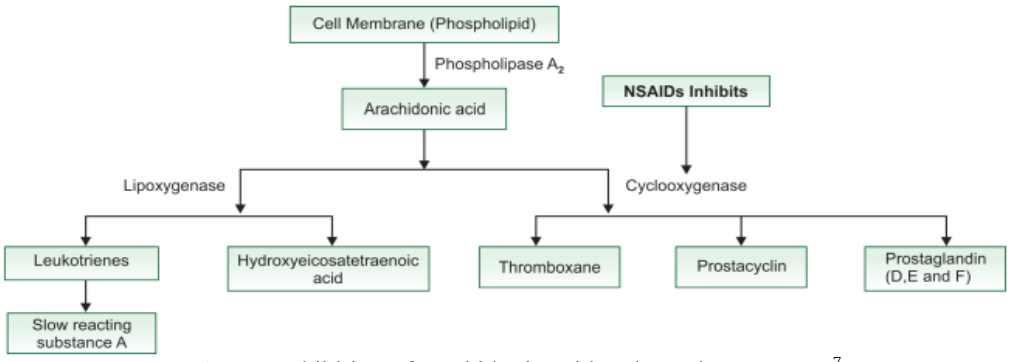


Figure: Inhibition of arachidonic acid pathway by NSAID's[7]

3) Modulation of Bone Metabolism

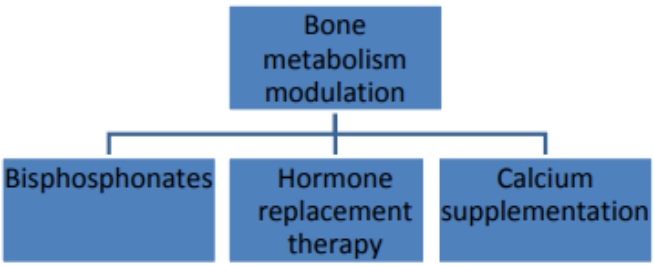


Figure: Modulation of Bone Metabolism

Following are the two molecules that are involved in regulation of osteoclast formation and process of bone resorption:

- Receptor activator of nuclear factor-kappa B ligand (RANKL).
- Osteoprotegerin

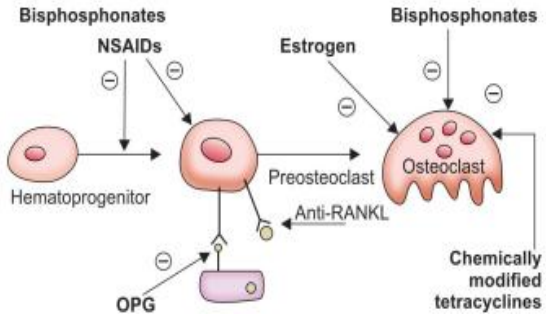


Figure: Action of bisphosphonates on bone resorption[7]

Bisphosphonate inhibits bone resorption by mainly acting on osteoclasts, mechanism of action of which is still unknown. They mainly decrease osteoclastic activity by inhibiting development of osteoclast and increasing apoptosis of the same. The main disadvantage of using bisphosphonate is bisphosphonate-related osteonecrosis of the jaw. Hence, they are also not approved as host modulation therapy till date.

4) Modulation of Nitric Oxide Synthase (NOS) activity

Nitric oxide (NO) is a highly sensitive free radical which is important in small amount for tissue homeostasis and host defenses, but it was found in excess amount in many inflammatory diseases which make it toxic & may lead to cytokine release, DNA and protein damage. Animal experiments that tested the inhibition of the isoenzyme nitric oxide synthase (NOS) by group of drugs e.g. mercapto-ethyl guanidine (MEGs); reduce inflammation, and bone loss. NOS inhibitors prevent alveolar bone resorption in experimental periodontitis. However further studies are needed to validates its beneficial effects in periodontal diseases[3].

5) Anti-Cytokine Therapy

Cytokines are defined as regulatory proteins controlling the survival, growth, differentiation and functions of cells. Cytokines are produced transiently at generally low concentrations, act and are degraded in a local environment. This is documented by the fact that cytokine-producing cells are often physically located immediately adjacent to the responding cells. Moreover, the responding cell destroys the cytokine that it responds to in the process of receptor-mediated endocytosis. Cytokines function as a network, are produced by different cell types and share overlapping features. This phenomenon is called biological redundancy[8].

6) Others

- **Aloe Vera**-It is a herbal product. It has many useful properties like antioxidant, anti-inflammatory, anti-microbial, immune boosting and healing properties. It is used as an adjunct to scaling and root planning treatment.
- **Probiotics**-Probiotics orally has proven to be useful for periodontitis patients. It decreases periodontal pathogens such as Candida albicans, Staphylococcus intermedius, Bacteroides, Actinomyces. They are used in periodontal dressings[10].
- **Hypochlorous acid and taurine-N-monochloramine**-They play an essential role in controlling the periodontal inflammatory process. They act together to alter the inflammatory responses by inhibiting the production of Prostaglandins and other pro-inflammatory substances[11].
- **Azithromycin**-Azithromycin is an antibiotic that is taken up into inflamed tissues by neutrophils and macrophages through chemotaxis. It is given per tablet of 500 mg for 3 consecutive days. It is effectively useful in the treatment of periodontitis as it has the ability to penetrate biofilm and has a long anti-bacterial half-life[12].
- **Cimetidine**-It is a histamine receptor antagonist that eliminates the inhibitory effects on immune response thereby acting as a modulator of inflammation and immunity, the neutrophil chemo-taxis, and superoxide production. They increase cyclic adenosine monophosphate levels and decrease the level of cytokine[11].

Various researches and reports have been put forward that showcase use of HMT with conventional scaling and root

planning is far better compared to only scaling and root planning. The summary of some of these are as follows:

Table 1: Study reports on MMP regulation[9]

Author	Interception	Conclusion
Caton et al. (2003) [13]	[10] SRP+SDD (20 mg)	SDD 20 mg bid for a period of 9 months showed significant clinical outcome and is not associated with any rebound effects or delayed or negative effects for a 3-month post treatment period.
Lee et al. (2004) [14]	SRP+SDD (20 mg)	SRP+SDD might be safe and effective in the management of chronic periodontitis.
Yan Xu, Wei Wei (2006) [15]	Experimented on rats in 4 groups— (1) model group (2) systemic sub antimicrobial dose of minocycline (5 mg/kg/day) treatment group (3) topical sub gingival dose of minocycline (2 mg/animal/week) treatment group (4) Control group.	Minocycline significantly reduced tooth mobility, gingival index and alveolar bone loss when administered either systemically or as a topical ointment compared to the model group.
Novak et al. (2008) [16]	Combination therapy of SRP+SDD –20 mg + locally delivered doxycycline 10%	Combination therapy provided significantly greater clinical benefits than SRP alone.
Preshow et al. (2008) [17]	Modified release sub-antimicrobial dose doxycycline (40 mg doxycycline)	SDD-40 mg +SRP resulted in significant clinical benefits than SRP alone.
Javali et al. (2012) [18]	Atridox delivery system (10% doxycycline hyclate)	Atridox is effective as SRP in reducing the clinical signs of periodontitis.

Table 2: Study reports on regulation of prostaglandin

Author	Interception	Conclusion
Heasman et al. (1993) [19]	1% w/w flurbiprofen tooth paste (b. i. d for 12 months)	Even though 1% w/w flurbiprofen toothpaste showed no apparent effect on clinical parameters, it exerts a small yet significant effect on bone metabolism.
Zeren et al. (2006) [20]	SRP + Ibuprofen (800 mg/day for 2 weeks	Adjunctive use of ibuprofen demonstrated no beneficial effect on the outcome of periodontal treatment of chronic periodontitis.
Yen et al. (2008) [21]	SRP + celecoxib (cyclooxygenase –2 inhibitor) 200 mg for 6 months	Celecoxib can be an effective adjunct to SRP to reduce progressive attachment loss in patients with chronic periodontitis.
Azoubel et al. (2008) [22]	SRP + Etoricoxib 120 mg/day for 7 days	Etoricoxib did not produce any clinical improvements but reduced PGE2 levels in GCF that could be related to the improvement in the bone condition.
Srinivas et al. (2011) [23]	SRP+1.5% ketoprofen (local drug delivery)	LDD+SRP were more effective in controlling periodontal disease than SRP alone.

Table 3: Study reports on modulation of bone metabolism

Author	Interception	Conclusion
Alencar et al. (2002) [24]	Oral administration of Disodium clodronate 2 mg/ kg in experimental periodontitis in rat model	Disodium clodronate decreases inflammatory changes and bone resorption in a periodontitis model in rats.
Yaffe et al. (2003) [25]	Combined application of alendronate + tetracycline hydrochloride 1%	Combined treatment reduced alveolar bone loss that might be due to the synergistic effect.
Ishii et al. (2003) [26]	Oral administration of incadronate (YM 175) 2 mg/kg in rats with experimental periodontitis	Results revealed that incadronate inhibits bone resorption and PMN migration periodontitis induced by P. gingivalis.
Goya et al. (2006) [27]	Topical administration of 100 µL 150 mm monosodium olpadronate	Monosodium olpadronate Drug effectively prevented bone loss and caused marked morphologic changes in osteoclasts.
Pradeep et al. (2012) [28]	Local drug delivery of 1% alendronate gel	1% alendronate gel resulted in significant reduction of PD, CAL gain, and improved bone fill.

Table 4: Study report on regulation of immune and inflammatory response

Author	Agents	Conclusion
Martuscelli et al. (2000) [29]	Recombinant human IL-11	Subcutaneous injection of rhIL-11 was able to slow the progression of attachment and radiographic alveolar bone loss in ligature induced beagle dog mode.

Table 5: Numerous recent experiments have been done in this field of dentistry, some of them are stated below:

Author	Interception	Conclusion
Hesham El Sharkawy et al [2010][32 30]	Subjects were administered SRP followed by dietary supplementation of fish oil (900 mg EPA + DHA) and 81 mg aspirin daily.	This demonstrated a significant reduction in probing depths and attachment gain after 3 and 6 months in the test group compared to placebo and the control group (P <0.05). Salivary RANKL and MMP-8 levels showed significant reductions in the test group in response to treatment compared to the control group at 6 months this resulted in a significant shift in the frequency of pockets with probing depths <4 mm (P<0.05).
Pooja Arora et al (2019) [31]	Two groups were formed: Group I-Control group (SRP + placebo gel), placebo gel was placed after SRP. Group II-Test group (SRP + SMV gel) = In which SMV gel was placed after SRP.	The 6 months clinical trial study was found to be statistically significant with greater reduction in PD, more CAL gain and greater intra bony defect fill at sites treated with SRP and Simvastatin than the SRP and placebo alone. So local application of SMV (1.2mg) is beneficial in treatment of chronic periodontitis along with SRP.
Widyastuti et al [2020] [32]	Lemuru fish oil gel in gingival sulcus of rats for 14 days	Lemuru oil showed significant gain in width of PDL and collagen density with optimal concentration.
Po-Chung Chang et al [2020][33]	Simvastatin (SIM) and doxycycline (DOX) were encapsulated in PLGA-chitosan nanospheres and delivered to sites of experimental periodontitis and large-sized mandibular osseous defects of rats for 1–4 weeks. SIM and DOX sustainably. SIM-DOX and SIM nanospheres could be considered to promote the repair of infected periodontal sites and non-infected osseous defects respectively.	DOX and SIM-DOX nanospheres significantly inhibited *P. gingivalis* and *S. sanguinis*. In experimental periodontitis sites, SIM-DOX nanospheres significantly down-regulated IL-1b and MMP-8 and significantly reduced bone loss. In mandibular osseous defects, VEGF was up-regulated, and osteogenesis was significantly augmented with SIM nanospheres treatment.
Hasanuddin Thahir et al [2021][34]	Used Omega 3 as HMT	Omega 3 fatty acids have positive effect on periodontal wound healing.

3. Conclusion

Host Modulation Therapy HMT has emerged as a promising adjunctive treatment for periodontal disease, enhancing therapeutic responses and slowing disease progression. Despite its potential, the awareness and application of HMT are still not optimal, partly due to the fact that only Periostat has received regulatory approval to date. While HMT could revolutionize periodontal treatment, more research is needed to understand the effects of various drugs used in HMT, mitigate their side effects, and gain wider regulatory approval. The integration of HMT with conventional treatments could lead to better clinical outcomes in periodontal disease management

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