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EFFECT OF PHARMACOLOGICAL AGENTS ON BONE REGENERATION

Dental Science

Dr. Koyalakonda Rohini* Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.*Corresponding Author

Dr. George Bibina Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

Dr. Anand Neha Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

Dr. Sreedevi Anusree Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

Dr. Kaleemi Hasan Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

Dr. Patil Veena Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

Dr. Mudda Jayashree Department of Periodontics and Implantology, H.K.E.S' S. Nijalingappa's Institute of Dental Sciences and Research, Kalaburagi, Karnataka.

ABSTRACT

The motive behind periodontal treatment is to prevent further attachment loss and regenerate the lost periodontal supporting tissues. To achieve this, various therapeutic strategies are available. Over the past two decades, a variety of pharmacological agents have been studied for regeneration of the lost periodontal structures. Host modulation therapy combined with the nonsurgical periodontal therapy has been of late considered as a new therapeutic option for the management of periodontal disease.

KEYWORDS

Pharmacological agents, Bone metabolism, Regeneration, Antibiotics, NSAIDS.

Introduction

Normal periodontium constitutes the gingiva, periodontal ligament, cementum and the alveolar bone. Several diseases affect the composition and integrity of periodontal structures causing the destruction of the connective tissue (CT) matrix and cells, the loss of fibrous attachment and the resorption of alveolar bone. These changes often lead to tooth loss.[1]

Bone is a mineralized connective tissue, with a unique trauma healing capability [2]. Osteoblasts, osteocytes and osteoclasts are the specialized bone cells. When a bone defect occurs due to injury, cells are supplied from the periosteum and the regeneration occurs [2,3]. However, satisfactory regeneration becomes more difficult the wider the bone defect. The reconstruction or restoration of osseous defects caused by inflammatory periodontal disease is a continuing challenge in periodontal therapy. Although many attempts have been made to regenerate alveolar bone support and the attachment apparatus, predictable success has been proved elusive [4].

Therapeutic modalities should aim not only in arresting and preventing the progress of periodontal tissue destruction but also at reestablishing and regenerating the periodontal tissues previously lost to disease. Agents that modulate the host response for periodontal repair and regeneration include, exogenous growth and differentiation factors, attachment factors which enhance the normal wound healing response that may be of insufficient magnitude to promote complete regeneration of all attachment structures.[5]

Host modulatory therapy has been proposed as a treatment for periodontal diseases. “Perioceutics” or use of specific pharmacologic agents to manage periodontal diseases is seen as an emerging trend when used in conjunction with mechanical debridement.

Antibiotics

Some of the antibiotics which have effect on bone metabolism are tetracyclines. Tetracyclines directly interact with matrix metaloproteins and cytokines thus preventing bone loss and promote bone formation. The study of Gomes et al. [6] evaluated the in vitro proliferation and activity of human bone marrow cells in an osteoblastic-inducing medium in different concentrations of doxycycline and minocycline during 35 days.

Besides tetracyclines, other antibiotics may have potential to participate in bone metabolism as clarithromycin (CLT). The use of this macrolide has been suggested to accelerate bone remodeling through antibacterial and anti-inflammatory properties. [7, 8] Moreover, some studies reported that clarithromycin exhibits anti-inflammatory properties. Based on these anti-inflammatory properties, Alenezi et al.[9] presented a study investigating the controlled release of CLT using poly (lactic-coglycolic) acid (PLGA) microspheres and BCP as a carrier in vivo. The results suggested that PLGA microspheres loaded with CLT group presented highest amount of bone formation, however only 12 weeks after the procedure. No increase in bone formation was observed in 2 and 4 weeks after the surgery, suggesting a long-term effect only.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-Inflammatory drugs (NSAIDs) originated as salicylate extracts in plants, as initially described in ancient Roman and Greek literature ; the willow tree extract was renowned for their antipyretic, analgesic, and anti-inflammatory properties.[11]. Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (derived from the cellular phospholipid bilayer by phospholipase A2). Prostaglandins acts as messenger molecules in the process of inflammation.[12,13] This mechanism of action was elucidated by John Vane in the 1970s earning him Nobel Prize for the same.[14]

It has been suggested that the anti-inflammatory action of NSAIDs is due to the inhibition of COX-2, whereas COX-1 inhibition is associated to unwanted effects related to interference of the regulatory and protective mechanisms [15,16].

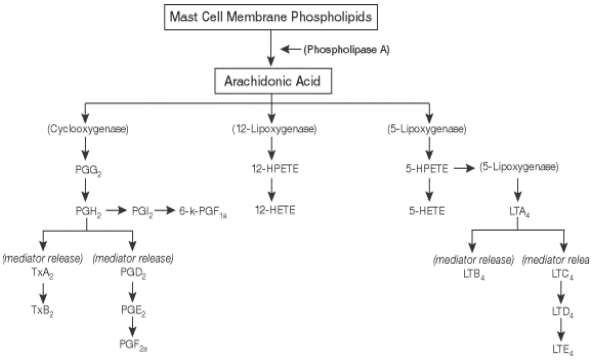

Fig-1: Arachidonic acid metabolites formation

Higher levels of PGE2 are associated with increased gingival inflammation and alveolar bone loss (Noguchi and Ishikava, 2007, Reynolds et al., 2007, Tripton et al., 2003) [17,18]. Use of NSAIDs results in decreased levels of pro-inflammatory mediators such as Arachidonic acid that may limit the host-mediated alveolar bone destruction observed in periodontitis and peri-implant disease.

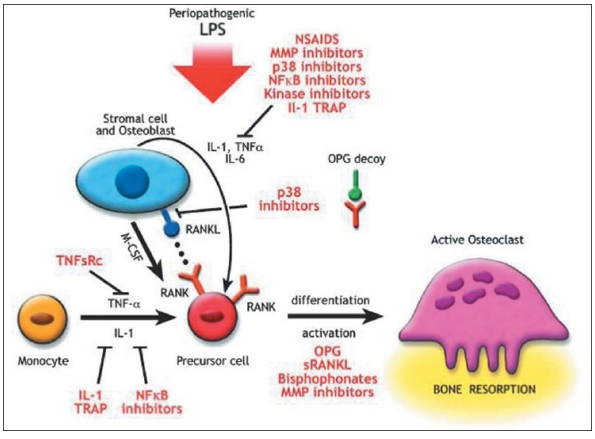

Figure 2: Mechanism of action of non-steroidal anti-inflammatory drugs – they inhibit the synthesis and release the synthesis of prostaglandins

Bisphosphonates:

This was introduced in the 1900s for the treatment of Osteoporosis and Osteolytic tumors. They are found to modulate alveolar bone resorption by inhibiting Osteoclasts via inhibition of bone turnover [19].It has greater affinity to mineral phase of bone due to its chelating properties for Calcium (Rogers et al,1999).

There are three generations of Bisphosphonates known to exist [20].
I : Etidronate (Alkyl side chain)
II : Alendronate (-NH terminal side chain)
III : Zoledronate (Cyclic side chain)

These are enzyme-resistant analogues of pyrophosphate that are bound to the matrix, released slowly and ingested by osteoclasts when they resorb bone. Alendronate acts in osteoclast cells, altering the cytoskeleton, thus inhibiting its interaction with bone matrix; prevents osteoclast recruitment, their differentiation and causes apoptosis of these cells [20].It also promotes osteoblastogenesis by initiating osteoblast precursor's formation, mineralized nodules and inducing secretion of inhibitors of osteoclast-mediated resorption by osteoblasts [21]. ALN promotes the enhancement of BMP-2, ALP, COL1 and osteocalcin (OCN) gene expression and the increase of ALP activity [22,24]. As side effects, hypocalcemia, atrial fibrillation and jaw necrosis are the most serious problems related with the usage of ALN, mainly with high IV dose application [23].

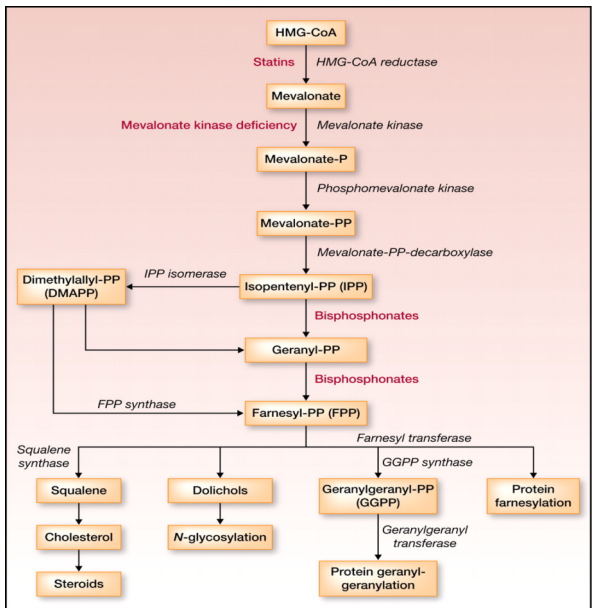

Fig-3: Mechanism of action of Bisphosphonates

Statins:

Reversible inhibitor of HMG-CoA reductase enzyme. Hence, also called as HMG-CoA reductase inhibitor. It has potential anti-inflammatory effect. The reaction catalyzed by HMG-CoA reductase and inhibited by simvastatin is the conversion of HMG-CoA to a compound called mevalonate via an intermediate. Simvastatin like the other statins is thus an inhibitor of the mevalonate pathway and consequently cholesterol synthesis [18].

Recent studies have shown its effects on new bone formation through increasing the expression of the BMP-2 gene in bone cells. However, less than 5% of the drug reaches the systemic circulation due to extensive first-pass metabolism in the liver as SV presents high liposolubility [25]. Potential pleiotropic effects of statins involve immunomodulatory, antioxidant, antithrombotic and endothelium stabilization actions, as well as angiogenesis promotion and increase of osteoblastic differentiation, inducing bone formation. In addition, statins can inhibit tumor cells growth and enhance intracellular calcium mobilization.

Primary effects of statins include inhibition of major histocompatibility complex II expression, binding of statins to leucocyte function associated antigen and preventing its binding to ICAM1 which leads to inhibition of its function in leucocyte adhesion and extravasation and thus, inhibition of release of proinflammatory cytokines mononuclear cells.

Conclusion:

The role of host responses modulated through genetics, immunological and inflammatory responses along with environmental factors play a major role in outcomes of periodontal disease. If periodontal disease is host mediated disruption of microbial homeostasis, then it stands to reason that by controlling the inflammation (mechanical + pharmaceutical), it should be possible to control the disease.

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