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Pharmacological Agents Influencing Bone Remodelling in Periodontics

[1]Dr. Vinita Boloor, Additional Professor, Department of Periodontology, Yenepoya (deemed to be university), Mangalore, Karnataka, India.

[2]Dr.Umme Kulsum, Post graduate, Department of Periodontology, Yenepoya (deemed to be university), Mangalore, Karnataka, India.

[3]Dr. Rajesh K.S, MDS, Professor and Head, Department of Periodontology, Yenepoya (deemed to be university), Mangalore, Karnataka, India.

[4]Dr. Shashikanth Hegde, Additional Professor, Department of Periodontology, Yenepoya (deemed to be university), Mangalore, Karnataka, India.

Corresponding Author: Dr. Umme Kulsum, Post graduate, Department of Periodontology, Yenepoya (deemed to be university), Mangalore, Karnataka, India.

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Introduction

Inflammation and bone loss are hallmarks of periodontal disease (PD). Accumulated evidence demonstrates that PD involves bacterially derived factors and antigens that stimulate a local inflammatory reaction and activation of the innate immune system. Pro-inflammatory molecules and cytokine networks play essential roles in this process. Interleukin-1 and tumor necrosis factor-alpha seem to be primary molecules that, in turn, influence cells in the lesion. Eventually, a cascade of events leads to osteo-clastogenesis and subsequent bone loss via the receptor activator of nuclear factor-kappa B (RANK)-RANK ligand (RANKL)- osteoprotegerin (OPG) axis.[1]

Bone is a remarkably dynamic and active tissue, undergoing constant renewal in response to mechanical, nutritional, and hormonal influences. A balance between the coupled processes of bone resorption by osteoclasts and bone formation by osteoblasts is required in a healthy adult. Under physiologic conditions, these processes are very carefully regulated by systemic hormones and local factors and orchestrated by osteocytes and bone lining cells which fine-tune interstitial fluid and plasma calcium levels.[2]

Drugs counteracting bone resorption, coined antiresorptive drugs (ARDs), interfere with bone metabolism with the aim to decrease abnormal bone remodelling and/or increased bone resorption. ARDs, despite differences in their mechanisms of action, in

general, decrease bone remodelling and resorption by inhibiting differentiation and normal function of osteoclasts (OCLs), and/or increase their apoptosis.[3]on other hand many of the drugs used in treating various systemic disorders can have a myriad of adverse effects on bone health, by interfering with vitamin D metabolism, interfering with vitamin D/calcium absorption, promoting calcium loss through urine, or by directly affecting osteoblastic or osteoclastic activity

Various Pharmacological Agents Inhibiting

Bone Loss/Antiresorptive Drugs

Antiresorptive treatments primarily target osteoclasts, reducing their lifespan or activity; they may have secondary effects on osteoblasts or osteocytes.

Bisphosphonates

Bisphosphonates (BPs) are pyrophosphate analogs that can suppress osteoclastic bone resorption. They are known to bind to hydroxyapatite crystals and prevent their dissolution in addition to increasing osteoblast differentiation and inhibiting osteoclast activation. Giannobile WV has summarized and categorized the bone-specific actions of bisphosphonates at *the tissue level* (decrease bone turnover due to inhibition of bone resorption, decrease the number of new bone multicellular units resulting in a net positive whole body bone balance) and at the *cellular level* (decrease osteoclast recruitment, osteoclast adhesion, depth of resorption site and release of cytokines by macrophages along with an increase in osteoclast apoptosis and osteoblast differentiation and number).[4-5]

Bisphosphonates have been used in a variety of bone disorders including osteoporosis, tumor-associated osteolysis, arthritis and periodontitis. Shoji *et al*. in 1995 demonstrated that systemic administration of a bisphosphonate could prevent alveolar bone resorption in rats with experimental periodontitis.[6] Studies in infrabony defects (Pradeep, Kanoriya, et al., 2017; Sharma & Pradeep, 2012a, 2012b; Sharma et al., 2017) showed a significantly higher reduction in Infrabony defect depth (ranging from 1.88 to 2.50 mm compared to 0.09 to 0.12 mm) and in percentage of defect depth reduction (ranging from 40.4% to 46.1% compared to 1.86% to 2.5%) 6 months after applying local bisphosphonates instead of placebo together with NSPT.[7]

Delivery of bisphosphonates as an adjunct to scaling and root planing in the management of periodontal disease appears to be effective in the short-term; however, due to the potential risk of osteonecrosis of the jaws, the use of bisphosphonates as an adjunctive treatment for periodontal disease is not indicated.[8]

Calcitonin

The peptide calcitonin (CT) was initially discovered in 1962 as a novel hypocalcemic hormone.[9] Calcitonin exerted its antiresorptive effects via directly reducing osteoclastic resorption, and thus increaseing bone mineral density and bone strength.[10] It was found that Calcitonin upregulated the expression of collagen type I and III and osteogenetic differentiation markers including osteocalcin and alkaline phophatase. CT regulate collagen synthesis and osteoblastic differentiation in hPDLFs by the same pathway as that activated by CGRP. Spolidorio et al. reported that CT inhibited cyclosporine A-induced alveolar bone loss via a decrease of circulating inflammatory cytokines, such as IL-1 and IL-6, in a rat model.[11]local administration of CT may have a highly anti-resorptive effect in experimental periodontitis rats.[12]

Denosumab

Denosumab was identified by Osteoporosis Canada Clinical Practice Guidelines as a first-line agent for treatment of postmenopausal osteoporosis. Denosumab

is a powerful anti-bone resorptive drug produced for treatment of osteoporosis patients who have a high risk for fracture, as well as development of cancer metastasis and giant cell tumors in bone tissue.[13]

The drug consists of human monoclonal antibodies that bind to receptor activator of nuclear factor κB ligand (RANKL), a tumor necrosis factor (TNF)-super family cytokine produced by osteoblasts and stromal cells in bone tissues.[14]

Denosumab inhibits bone destruction caused by enhanced differentiation and function of osteoclasts by interrupting RANKL and RANK interactions.[15] Jin et al. (2007) demonstrated that systemic delivery of OPG-Fc fusion protein inhibits alveolar bone resorption in experimental periodontitis, supporting the fact that RANKL inhibition may represent an important therapeutic strategy for the prevention of progressive alveolar bone loss.[14] In periodontitis model mice, where the second molars were ligated with a silk suture to induce inflammation, intraperitoneal administration of anti-RANKL antibodies significantly inhibited alveolar bone destruction and tooth root exposure.[16]There are concerns that the use of RANK／RANKL inhibitors can inhibit both physiological and inflammatory bone resorption and may have an unwanted systemic effect on bone.

Host Modulating Agents Acting Against Arachidonic Acid Metabolites

Free arachidonic acid (AA) is produced in the hosts when phospholipase A2 acts on the phospholipids present in plasma membranes of the cells which can then be metabolized to produce prostaglandins via the cyclooxygenase (COX) pathway as well as leukotrienes via the lipoxygenase (LOX) pathway.[17] Dybvig et al validated that prostaglandins are an important mediator of bone loss in periodontitis.[18] Non-steroidal anti-inflammatory (NSAIDs) drugs block the activity of both cyclooxygenase isozymes (COX-1 and -2) and many authors have demonstrated the role of NSAIDs like flurbiprofen, indomethacin, and naproxen, in inhibiting gingivitis and progression of periodontitis.[19]

A large number of animal studies and longitudinal clinical trials were conducted in which patients received daily administration of oral nonsteroidal anti-inflammatory drugs for extended periods of time (up to several years). In broad terms, a generally consistent finding was that the rate of alveolar bone loss was reduced compared with patients who were taking placebo. However, a high rate of unwanted effects was also noted, and a further problem was that patients needed to take the drugs on a daily basis for several years for the beneficial impact on bone loss to become apparent. To summarize, the nonsteroidal anti-inflammatory drugs (including both the nonselective, nonsteroidal anti-inflammatory drugs and the selective cyclooxygenase-2 inhibitors) have been extensively investigated for use as adjunctive anti-inflammatory treatments for periodontitis, but limited clinical benefits, together with a significant risk of serious unwanted effects, precludes their use as a drug treatment for periodontitis.[20]

Hormonal Therapy

- **Parathyroid hormone (PTH)**

Parathyroid hormone (PTH) plays an essential role in regulating phosphorous (P) and calcium (Ca) levels during bone remodelling.[20]PTH has been used in the treatment of osteoporosis to increase bone density and prevent fractures. The mechanism of the PTHs action is complex and involves pathways linked to common signaling peptides that affect osteoblast gene transcription. Yoshida W et al demonstrated that systemic intermittent administration of PTH in

combination with local application of the SAP(self-assembling peptide) nano-fibre hydrogel SPG-178 promoted periodontal healing in vivo.[21]

Teriparatide

It is a recombinant form of PTH consisting of the first 34 amino acids of PTH. Since it is identical to a portion of human PTH, it is known as biosynthetic human PTH. It is a highly potent anabolic (i.e. bone growing) agent and most commonly used in the treatment of osteoporosis. The biological actions of teriparatide and PTH are mainly activated through specific, G-protein-dependent, high-affinity membrane cell-surface receptors. These receptors are mainly demonstrated in osteoblasts and renal tubular cells. It has been demonstrated that ligand binding promotes a cascade that energize protein kinase-1, protein kinase C, cyclic adenosine monophosphate (cAMP) and phospholipase C. The activation of these pathways results in an up-regulation of the number of active osteoblasts, a down-regulation in osteoblast apoptosis and probably, increase of bone lining cells as newly formed osteoblasts, thereby enhancing bone strength, structural integrity, mass and diameter, as well as increasing serum and urinary levels of markers of bone resorption and formation. Teriparatide, as compared with placebo, was associated with improved clinical outcomes, greater resolution of alveolar bone defects, and accelerated osseous wound healing in the oral cavity.[22]

Estrogen AND Selective estrogen receptor modulators (SERMs)

The mechanism by which SERMs inhibit bone resorption is likely to be the same as estrogen's mechanism, by blocking production of cytokines that promote osteoclast differentiation and by promoting osteoclast apoptosis.[23]Inagaki *et al*. has also suggested the use of selective estrogen receptor modulators (SERM) and hormone replacement therapy (HRT) to improve the clinical outcome of periodontal disease as an adjunctive treatment to preserve periodontal bone mass. Shu *et al*. in 2008 also demonstrated in human periodontal cells that estrogen may play a significant role in modulating periodontal tissue responses to lipo-polysaccharide, and may exert its bone-sparing effects on periodontal tissues *via* altering the expression of inflammatory cytokines.[17]

Cathepsin K Inhibitors

The enzyme cathepsin K is a cysteine proteinase of the papain superfamily, which is selectively expressed in osteoclasts and plays a pivotal role in the degradation of bone matrix. It is the only known mammalian proteinase that can solubilize both type I and II collagens by cleavage of the telopeptide region.[14] The key role of cathepsin K in bone resorption makes the protease an attractive therapeutic target in disorders where bone resorption is excessive, e.g. osteoporosis and in joint diseases involving bone, such as osteoarthritis (OA). Cathepsin K has been identified in periodontal tissues and in gingival crevicular fluid. Increased concentrations of cathepsin K have been detected in the gingival crevicular fluid from patients with periodontitis, which correlated with an increased concentration of RANKL, suggesting that both contribute to osteoclastic bone destruction in periodontal disease.[24]Accordingly, cathepsin K has been viewed as an attractive target for modulating bone resorption. Odanacatib, a cathepsin k-specific inhibitor, prevents bone loss and the immune response during the progression of periodontitis. [25]

IKK- β INHIBITION

IKK- β also known as inhibitor of nuclear factor kappa-B kinase subunit beta is activated following the binding of RANK to RANKL. As such, this process is a target for the inactivation of nuclear factor-kappa B activation

because IKK- β is essential for nuclear factor-kappa B activation by proinflammatory cytokines. Oral administration of a selective potent inhibitor of IKK- β has demonstrated both anti-inflammatory and anti-bone-resorbing effects in an animal model. Hence, the dual effect of inhibiting inflammation and inhibiting bone resorption indicates some potential for this drugs.[14] IMD-0354 is a novel I kappa-B kinase (IKK) inhibitor, which regulates inflammation. IMD-0354 regulated bone resorption by ligature-induced periodontitis, and it is suggested that the inhibition of IKK via down-regulation of NF kappa-B may provide periodontal patients with an effective approach to prevent or suppress the disease.[26]

Vitamin D And Calcium

The importance of vitamin D and calcium for bone health is well known. Vitamin D, which is derived from dietary sources and the action of sunlight, is essential for bone formation. Vitamin D helps regulate the amount of calcium and phosphate in the body. There are numerous studies confirming that vitamin D deficiency is associated with bone loss. daily oral treatment with calcium gluconate (for 10 days) effectively inhibits ligature-induced periodontitis and related alveolar bone loss via antioxidant effects.[27]Oral administration of Polycal (a 2:98 (g/g) mixture of Polycan and calcium gluconate) has favorable synergic effects on ligation-induced periodontitis and topical application of Polycal has significant inhibitory effects on periodontitis and related alveolar bone loss in experimental periodontitis model through the antibacterial, anti-inflammatory and anti-oxidative activities.[28]

Tetracyclines

Tetracycline with antibiotic activity consists of a tetracyclic naphthacene carboxamide ring system having a dimethylamine group at carbon 4 (C4) in ring "A" which is responsible for its antibacterial property. About 3 decades ago, Golub *et al*. discovered that tetracyclines and its analog have the unexpected ability to inhibit MMPs, by mechanisms unrelated to its antibacterial properties.[17] Golub and McNamara *et al*. synthesized a chemically modified tetracycline (CMT) by removing the dimethylamino group from the carbon-4 position of the "A" ring, resulting in the 4-de dimethylaminotetracycline, i.e. CMT, which eliminated the drug's antimicrobial efficacy but did not reduce the ability of the drug to block the activity of collagenases.[16] SDD (Periostat®) is currently the only FDA approved MMP inhibitor that can be used as adjunct to NSPT. Recently, the American Dental Association reported that SRP alone and SRP combined with SDD for 3–9 months are the most evidence-based treatments for periodontitis. The 20 mg twice per day dose exerts its therapeutic effect by enzyme, cytokine, and osteoclast inhibition, rather than by any antibiotic effect.[7] Along with antimicrobial activity, tetracycline agents have the ability to inhibit neutrophils, osteoclasts, and matrix metalloproteinases (MMPs) that appear to be involved in the destruction of the periodontium. Tetracyclines have an anti-inflammatory action and may be bone-sparing through inhibition of osteoclasts.[23]

Statins

Statins are 3-hydroxy-3-methylglutaryl-CopA (HMGCoA) reductase inhibitors – have been widely used to prevent cardiovascular disease through controlling lipid metabolism. In addition to their capacity to reduce serum cholesterol levels, statins also possess significant anti-inflammatory properties. One of the most common statins is simvastatin, which has shown interesting results regarding the control of alveolar bone loss by simvastatin. Although two studies have questioned any beneficial effect of simvastatin on periodontal bone loss,[27-28] several studies have

demonstrated protective features with concerning periodontitis and alveolar bone loss.[29-30] Most recently the dual effect of statin medications on the periodontium was demonstrated to be dependent on the inflammatory status of the periodontal tissues.[31] Overall, these studies indicate that statins may have some beneficial therapeutic benefits for the periodontium through their immunomodulatory, anti-inflammatory and reduced bone-resorptive actions.

Wnt / β-Catenin Pathway Antagonists

A number of reports have indicated that the Wnt canonical pathway and the transcription factor activator protein-1 are important for the regulation of osteoprotegerin production in osteoblasts.[32] It has been proposed that the net production of osteoprotegerin in these cells depends on the interplay between the activation by the Wnt canonical pathway and the suppression by the transcription factor activator protein-1.[33] Within this process, beta-catenin plays an important role in the Wnt signalling pathway and in bone remodeling. The relationship between Wnt signalling and activator protein-1 in osteoprotegerin production has been demonstrated in the periodontal ligament and in gingival fibroblasts.[34] It was shown that beta-catenin could enhance interleukin-1alpha-induced osteoprotegerin production, and activator protein-1 suppressed interleukin-1alpha-induced osteoprotegerin production in periodontal ligament cells. Furthermore, a high expression of c-Fos (a component of the activator protein-1 transcription dimeric complex) has been reported in periodontal ligament cells compared with gingival fibroblasts, and this suggests a role for periodontal ligament fibroblasts in alveolar bone resorption in periodontitis. Because the Wnt pathway seems to form an important link between inflammation and bone metabolism, it provides a novel target for treating bone-erosive conditions by changing the balance between bone formation and bone resorption.[14] A glycoprotein that can inhibit the Wnt pathway is Dickkopf-1 (DKK-1). Osteopenia and osteoporosis have been reported when DKK-1 is overexpressed in osteoblasts.[35]

Sclerostin (SOST) is a secreted glycoprotein and an important regulator of WNT signaling in bone metabolism. SOST is primarily expressed by osteocytes and binds to lipoprotein receptor-related protein (LRP) 5/6 on the osteoblasts. SOST decreases osteoblastogenesis and osteoblastic activity antagonizing the WNT signaling pathway. Interestingly, SOST can also activate the “receptor activator of NF-κB ligand” (RANKL), promote osteoclast differentiation and bone resorption. Due to this dual anti-osteoblastic and pro-osteoclastic activity, targeting SOST with monoclonal antibodies enhances bone formation and increases bone mass and bone strength.[36] Taut et al. conducted a study to evaluate the therapeutic potential of Scl-Ab in alveolar regeneration in experimental periodontitis and demonstrated that Scl-Ab exerts an anabolic effect on alveolar bone both physiologically and therapeutically after experimentally induced periodontitis. It also reversed alveolar bone loss in a preclinical animal model of periodontitis.[37] Animal studies have demonstrated that Scl-Ab enhances osseointegration and bone regeneration around dental implants and improves trabecular bone volume and architecture.[38-39] Yao et al. conducted a study comparing the efficacy of systemically and locally administered Scl-Ab in rats with experimentally induced periodontitis and observed that systemic Scl-Ab significantly improved alveolar bone and cemental regeneration compared to locally delivered Scl-Ab.

Protease-Activated Receptor 2 Agonists/Antagonists

Protease-activated receptors are a group of related G protein-coupled receptors which are activated following proteolytic cleavage of their extracellular domain and play important roles in chronic inflammation. Four protease-activated receptors have been identified, of which protease activated receptor 2 has received particular attention regarding bone resorption. Activation of this protein results in the release of a variety of prostanoids and cytokines, including interleukin-6 and interleukin-8.[14] A potential role for protease-activated receptor 2, which can be activated by Porphyromonas gingivalis gingipains, in periodontitis has been suggested on the basis of its expression by alveolar bone osteoblasts, gingival fibroblasts and gingival epithelial cells.[40-41] However, there is conflicting evidence regarding the role of protease-activated receptor 2 in osteoclastogenesis and bone resorption. For example, one study has shown that protease activated receptor 2 activation can inhibit bone resorption through inhibiting osteoclast differentiation.[14]

Histone Deacetylase Inhibitors

Histone deacetylases are a group of enzymes emerging as potential targets for a number of diseases, including those involving pathological bone resorption.[42]The properties of histone deacetylases include inhibition of angiogenesis, inhibition of the production of proinflammatory cytokines and also protective effects on bone. Histone deacetylase inhibitors have been studied in animal models of rheumatoid arthritis where they were shown to reduce bone destruction. histone deacetylase inhibitors have the potential to provide another therapeutic module for the management of pathological bone loss and therefore further studies are warranted on these agents.[43]

In the context of periodontal pathogenesis is the finding that some histone deacetylase inhibitors appear to be able to regulate the effects of RANKL on osteoclasts and inflammatory cells, resulting in inhibition of RANKL-induced osteoclastic activity in mouse macrophages and murine cell lines. The inhibition of RANKL-induced osteoclast formation occurred via suppression of induction of the osteoclastogenic transcription factor, c-Fos. In a murine experimental periodontitis model, topical application of a novel histone deacetylase inhibitor resulted in a significant reduction in P. gingivalis induced alveolar bone loss, which occurred despite the inhibitor having no effect on reducing inflammation.[44]

Tumor Necrosis Factor-Alpha Inhibotors

Tumor necrosis factor-alpha is produced by activated macrophages as well as by many other connective tissue cells such as synoviocytes and periodontal fibroblasts. It used to treat diseases like rheumatoid arthritis (RA), juvenile arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, ulcerative colitis (UC), and Crohn's disease. Tumor necrosis factor-alpha has been reported to act either directly on osteoclasts or indirectly to induce osteoclast formation through the stimulation of RANKL production by osteoblasts. Because tumor necrosis factor-alpha can influence osteoclast formation in the presence or absence of RANKL it is a potential therapeutic target to control pathologic bone loss.[1] Over-expression of tumor necrosis factor-alpha has been associated with osteoclastogenesis in patients with periodontitis, and tumor necrosis factor antagonists have been shown to inhibit the inflammatory response and bone loss in experimental periodontitis. However, more recently, results from studies investigating the effects of tumor necrosis factor-alpha inhibitors on periodontal parameters have produced conflicting results.[14]

Medications currently available are Adalimumab -human monoclonal antibody, Cetrolizumab pegol-humanized tumor necrosis factor-alpha antibody, Entanercept - Tumor necrosis factor receptor (p75): Fc1IgG construct, Golimumab -Fully human monoclonal tumor necrosis factor-alpha antibody, Infliximab -chimeric monoclonal antibody, Atacicept -a recombinant fusion protein that binds and neutralizes B-lymphocyte stimulator and a proliferation-inducing ligand.[14]

Interleukins

Apart from tumor necrosis factor-alpha a large number of other inflammatory cytokines are involved in inflammatory diseases associated with bone loss and have therefore become logical targets for the development of therapeutic agents. One of the first cytokines to be targeted was interleukin-1 as a result of its key regulatory role in bone resorption in diseases such as rheumatoid arthritis and periodontitis. In addition to interleukin1, agents targeting interleukin-3, interleukin-6, interleukin-15 interleukin-12 and interleukin-23 have been studied. These anti-cytokine agents provide new opportunities to modulate host responses in inflammatory diseases. In particular, most seem to influence the secondary effects of cytokines on RANKL expression and therefore may not influence osteoclast-mediated bone resorption directly.[14] Few studies have investigated the effect of interleukin antagonists on periodontitis, such as **Anakinra**: a recombinant nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra) ,**Canakinumab**: recombinant, human anti-human-interleukin-1 monoclonal antibody that belongs to the IgG1/j isotype subclass. **Tocilizumab**: interleukin 6 (IL-6) receptor-inhibiting monoclonal antibody, **AMG714**: human monoclonal antibody against interleukin-15, **Ustekinumab**: human monoclonal antibody directed against interleukin-12 and interleukin-23.[14] Martuscelli *et al*. demonstrated that subcutaneous injections of recombinant human IL-11 (rh IL-11: anti-inflammatory cytokine) were able to slow the progression of attachment and radiographic alveolar bone loss in a ligature-induced beagle dog model.140

Strontium Ranelate

Strontium is a soft, silver-white metallic element deposited mainly in areas where mineralization of new bone takes place, such as regions undergoing intramembranous or endochondral ossification. Strontium ranelate (SR) is a dual-acting agent that reduces bone resorption by reducing osteoclastic activity and stimulating bone formation by stimulating preosteoblast replication.[45] Strontium ranelate is a medication used for the management of severe osteoporosis in high-risk postmenopausal women and adult men. SR binds to hydroxyapatite crystal surfaces such as calcium and has a critical role in bone mineralization process. There are two possible mechanisms of action presented in literature about SR: 1) activating calcium-sensing receptor or another cation-sensing receptor; and 2) increasing expression of OPG in addition to decreasing RANKL expression by osteoblasts.[46]

A study Investigating the Effects of Systemically Administered Strontium Ranelate on Alveolar Bone Loss Histomorphometrically and Histopathologically on Experimental Periodontitis in Rats. SR was found to be effective in reducing RANKL-mediated osteoclastic activity and preventing alveolar bone loss with the most effective dose of 900 mg/kg.[47]Another study demonstrated the effects of strontium ranelate on ligature-induced periodontitis during conditions of estrogen deficiency. Results demonstrated that treatment

with 625 mg/kg/d strontium ranelate counteracted alveolar BL by ligature in the initial (10 days), middle (20 days), and late phases (30 days), and yielded an overall higher trabecular bone area, especially under estrogen deficiency. The benefits of strontium ranelate in alveolar bone were subtler in the presence of normal levels of estrogen. Furthermore, the expressions of markers of bone turnover in ligated teeth were affected by the administration of this medication, suggesting that the anti-resorptive action of strontium ranelate may have constrained bone loss.[48]

Modulation of Nitric Oxide Synthase

Nitric oxide is a free radical with important physiological functions of maintaining homeostasis. While homeostasis requires low nitric oxide tissue levels, pro-inflammatory stimuli such as endotoxins leads to increased expression of the inducible nitric oxide synthase enzyme (iNOS), which acts beneficially for the host as a cytotoxic molecule against the invading microorganism, yet, it may also cause deleterious effects to host such as DNA damage, lipid peroxidation, protein damage, and stimulation of inflammatory cytokine release.[17] Lohinai et al. (1998) demonstrated the protective effects of mercaptoethylguanidine (MEG), which is a selective inhibitor of iNOS, against bone destruction in ligature-induced periodontitis in the rat.[49] Leitao et al. (2005) also proved that NOS inhibitors prevent alveolar bone resorption in experimental periodontitis.[50] A study demonstrated NOS inhibitor aminoguanidine hydrochloride 10 mg/kg/d was effective in inhibiting the inflammatory bone resorption in an experimental periodontitis model.[51]

Curcumin

A dietary herbal ingredient derived from turmeric, has historically been advocated as a safe and effective treatment for a variety of diseases. However, it has long been known that this compound's insolubility and poor absorption by the oral route has limited its clinical application. Recently, Stony Brook University laboratories (Oral Biology and Chemistry departments, Dr. Francis Johnson) have synthesized, developed, and tested a series of novel chemically modified curcumins with various side chains added to the carbon-4 position of this biphenolic compound.[52] Chemically modified curcumin-2.24 exhibiting superior efficacy compared to curcumin or chemically modified curcumin-2.5 as an inhibitor of inflammatory mediators and matrix metalloproteinases, this novel compound was found to be even more effective in reducing alveolar bone loss in vivo. In this regard, Guimarães et al[53] reported that although curcumin was effective in suppressing inflammatory mediators in the rat model of lipopolysaccharide induced periodontal disease, natural curcumin had no effect on alveolar bone loss, an observation that was later confirmed.[54] Elburki et al, in a preliminary study using the same rat model of periodontitis, found that pathologic alveolar bone loss was completely prevented by orally administered chemically modified curcumin-2.24. This dramatic effect on periodontal bone loss in vivo was associated with suppression of the proinflammatory cytokine, interleukin-1beta, and reduced levels of pro and activated forms of leukocyte-type gelatinase (matrix metalloproteinase-9) in the gingival tissues.[55-56]

Hyaluronic Acid (HA)

HA is a polysaccharide (glycosaminoglycan), it has a high molecular weight and has a major role in the activity of extracellular matrices, including those of non-mineralized and mineralized periodontal tissues. It is also produced in the presence of endotoxins by fibroblasts, and it plays a crucial anti-inflammatory role

by facilitating healing and inhibition of tissue destruction.[23]

Various Pharmacological Agents Inducing Bone Resorption/Loss

Drugs used in treatment various systemic disorders can have a adverse effects on bone health, by interfering with Vitamin D metabolism, interfering with Vitamin D/calcium absorption, promoting calcium loss through urine, or by directly affecting osteoblastic or osteoclastic activity and by causing altered hormone states which, in turn, promote bone loss (hypogonadism, hyperthyroidism, somatostatin excess states, insulin deficiency, increased systemic inflammation, and oxidative stress). These drugs are as follows.

Drugs Used In Neurological Disorders

Epilepsy is one of the most common chronic neurologic conditions and is frequently treated using long-term mono or polytherapy with antiepileptic drugs (AEDs) to prevent seizure. There is accumulating evidence of biochemical abnormalities indicating a disturbed bone metabolism, a decreased bone density and a 2 – 6 times increased risk of fractures among those with epilepsy compared to the general population. Enzyme-inducing drugs, such as phenytoin, phenobarbital and carbamazepine, but also the enzyme inhibitor valproate, appear to have bone-depleting properties. Reduced bone density may be detected during the first 1 – 5 years of treatment.[57] Although the risk of bone loss/fracture is considerably higher with the long-term use of phenytoin in the absence of vitamin D supplementation[57], low doses of phenytoin induces proliferation and differentiation of human bone cells to stimulate bone formation. When administered locally and released at a controlled low concentration, phenytoin-loaded PLGA microspheres promoted alveolar bone formation with increased expression of osteogenic markers. These findings indicate that phenytoin possesses dual effects on bone turnover that are dependent on the route of administration and dosage. The osteogenic stimulation effect of phenytoin is dose-dependent, being the most optimal at 5–50 μM in the in vitro setting ; osteogenic stimulation also requires long-term delivery of the medication at low concentrations.[58]

Drugs Used In Gastrointestinal Disorders

Proton pump inhibitors (PPIs) find a widespread and often over-the-counter use for various gastrointestinal disorders. Various hypotheses have been proposed for the mechanism of PPI-induced bone loss, the most popular of these is the reduced intestinal absorption of calcium and magnesium which is seen with prolonged PPI use because of interference with the acidic gastric environment. PPI use may also lead to Vitamin B12 deficiency, which could lead to neuropathy and hence increased risk of falls and fractures. However, various confounding factors may come into play, such as age-related bone decline and comorbid illnesses, which is noteworthy as the maximum consumption of PPIs is seen in the aging population.A study by Brendon et al (2020) concluded that PPI medications are related to more loss of crestal bone at implant sites.[59] A study investigated the possible PPI-induced bone changes in the mandible on panoramic radiographs with the methods of fractal analysis and panoramic morphometric indices which concluded the use of PPI has been associated with osteoporotic changes in the trabecular and cortical bone structure of the mandible in the premolar teeth area.[60] A judicious and vigilant prescription of PPIs, with the use being limited to the lowest possible dose and for the shortest possible duration. Over-the-counter use of PPIs should be strongly discouraged. Those individuals who are on

long-term PPI treatment must be offered calcium and Vitamin D supplementation under supervision.

Drugs Used In Rheumatology And Immunology

Glucocorticoids (GCs) also find wide use in the management of rheumatological disorders but are associated with a myriad of adverse effects on bone health. The mechanism includes direct suppression of osteoblasts, enhanced RANKL activity leading to augmented osteoclastic resorption, reduced intestinal calcium absorption, and hypercalciuria leading to secondary hyperparathyroidism.[6] A study showed that glucocorticoid-induced osteoporosis worsens the alveolar bone loss in rats with experimental periodontitis. GCs increase the expression of the macrophage colony stimulating factor (M-CSF) and RANKL, and decrease the expression of its soluble decoy receptor, osteoprotegerin, in stromal and osteoblastic cells. It leads to osteoclastogenesis and a prolongation of the lifespan of osteoclasts. In addition, it has been reported that, when inflammatory disorders such as periodontitis are present, GCs may potentiate the resorptive process.[61] In a study, long-term GCs administration in mice led to a decrease in alveolar bone (represented in the mouse by alveolar processes connected with a bony slab between the incisor and the molar roots). Even if alveolar bone is low in the mouse, GCs induced a reduction of bone volume in the processes; furthermore, thinning and perforations occurred in the thin slab of underlying bone.[62]

Calcineurin inhibitors, including cyclosporine A (CsA) and tacrolimus, have been widely used as immunosuppression to prevent organ transplant rejection and for autoimmune disorders. Both are associated with bone loss and increased fracture. In vitro, calcineurin inhibitors inhibit osteoclastogenesis and osteoclast activity via reductions in Nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1). However, in animal models and humans, these drugs cause dose and duration-dependent bone loss with excessive osteoclastogenesis. [62]

Anticoagulants

The adverse effects of warfarin on bone health are directly related to the duration of treatment, with a significant deterioration seen only with a therapy lasting for >1 year.[6]. Mechanistically, warfarin decreases the γ carboxylation and calcium-binding properties of osteocalcin and is predicted to negatively impact BMD [Lian and Gundberg, 1988]. Many small cross-sectional and retrospective studies indicate that warfarin is associated with reductions in BMD and increases in vertebral and rib fractures [Fiore et al. 1990; Philip et al. 1995; Caraballo et al. 1999]. However, other studies have found no significant effects on BMD or fractures in warfarin users compared with controls [Piro et al. 1982; Jamal et al. 1998; Woo et al. 2008].[62]

Heparin is yet another commonly used anticoagulant. Although its short-term use is not associated with reductions in BMD or increased fractures, its long-term use may lead to these complications. Mechanistically, unfractionated heparin inhibits osteoblast differentiation and function, leading to decrease in bone formation. In addition, heparin increases bone resorption by leading to reductions in osteoprotegerin (OPG), favoring RANKL-induced osteoclast differentiation.[61]

Drugs Used In Endocrinology

The impact of diabetes as well as oral antidiabetic drugs (OADs) on BMD and fractures has been reported in a few studies over the last couple of decades. Among all the classes of OADs**, thiazolidinediones** are the most notorious for their adverse effects on BMD. Pioglitazone, a thiazolidinedione antidiabetic agent, promotes adipocyte differentiation into smaller and

insulin-sensitive adipocytes as a trade-off for osteoblast formation. This suppressed osteoblast formation has a detrimental effect on bone health and increases fracture risk. In a meta-analysis involving 22 randomized controlled trials, a statistically significantly increased incidence of fracture was found in women on thiazolidinediones.

Drugs Used In Infectious Diseases

HIV-1 infection is associated with upregulation of pro-inflammatory cytokines (e.g., TNF-α), which can lead to increased osteoclastic activity and hence bone resorption.[168-169] The risk of poor bone health is further compounded by antiretroviral therapy. Disturbed Vitamin D metabolism, i.e., an increased vitamin degradation due to induction of CYP3A4, appears to play a major role. In a study of 1077 HIV-infected patients, the risk of severe Vitamin D deficiency was significantly increased by the intake of the non-nucleoside reverse transcriptase inhibitor efavirenz.[61]

Drugs Used In Oncology

Doxorubicin, commonly used in different combination for the treatment of childhood hematologic cancers and solid tumors, is associated with impaired bone architecture, leading to bone mineral loss. Hypogonadism in any form is associated with increased bone mineral loss and fractures due to loss of trophic effect of sex steroids on bone mineral health. Platinum-based chemotherapy agents such as cisplatin cause hypomagnesemia, which can lead to the suppression of osteoblast activity and inhibition of bone formation. Some chemotherapeutic agents are associated with excessive bone loss. High-dose methotrexate can directly cause bone loss.[62]

Conclusion

Use of the pharmacological agents specifically developed to manage periodontitis is an interesting and emerging aid in the management of periodontal disease along with the mechanical debridement. Understanding of the host-bacterial interactions and the host immuno-inflammatory response leading to periodontal tissue destruction has led to the development of host modulation therapy. Furthermore, continuous research in this field would also enable fabrication of individualized treatment for periodontal disease targeting inflammatory host response. An increased awareness of the medications which are linked with impaired bone health, minimizing the use of them in patients who are at an higher risk, keeping the dosage as well as duration of therapy to as low as possible, ensuring Vitamin D and calcium adequacy either through diet or supplements can play a major role in preventing adverse effects associated with drug-induced bone loss.

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