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An anti-anabolic drug for future periodontal regeneration- A current update

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Abstract

As we all know that periodontitis is a chronic in flammatory infectious disease of tooth supporting tissues associated with dys biotic dental biofilm. There is an imbalance between microbiota & host cells that may release the pro-in flammatory cytokine cascade with activation and differentiation of specific type of immune cell leading to progressive loss of periodontal attach Ment, bone loss & eventually tooth loss. There is also an alteration in osteoblast and osteoclast cell activity resulting from periodontitis and causing bone resorption. Therefore, a number of drugs have been used non surgically as an adjunct to periodontal therapy to maintain the homeostasis of bone cells. Teriparatide ia an effective bone anabolic agent which is available in recombinant as well as synthetic form of human parathyroid. It has a promising application in the field of dentistry. Teriparatide agent increases the bone formation, maintaining bone homeostasis and density, bony microstructure such as increase in number of bony trabeculae and thickness as well as reduces the bone fracture. Currently, clinical trials and studies with teriparatide have been going on periodontal and osseous regeneration which may show an excellent result especially in osseous defects. Teriparatide agents open a future door for periodontist especially in the field of periodontal regeneration. This review highlights the possible application of this novel agent in periodontal disease and regeneration.

Keywords: Anabolic Agent, Teriparatide, Regeneration, Periodontitis, Parathyroid hormone related peptide (PTHrP).

Introduction

Periodontitis and dental caries are the two principal dental diseases that affect the human population at high prevalence rates worldwide.[1] Recent data indicate that a prevalence of Periodontitis in adults in the United States estimates that 47.2%, or 64.7 million American adults have the mild, moderate, or severe form of the disease.[2] Around 10% of patients with periodontal disease progress into the severe category.[3] Hence, the prevention and treatment of periodontitis is of utmost importance, particularly in the field of dentistry. The periodontium is a complex structure that must remain in biologic harmony in order to maintain a healthy state. During the in flammatory process of Perio dontal disease this harmony is interrupted, and commensal bacteria begin to take advantage. Periodontitis is an aggressive pathology of concern since it alters the integrity of the periodontal system, eventually involves the destruction of the periodontal ligament and alveolar process, which when left untreated can ultimately lead to tooth loss.[4,5] The goal of periodontal therapy is to provide patients with a dentition that is functionally healthy and pain free for the rest of their lives. The preservation of the natural dentition may be achieved by reducing or controlling the tissue inflammation induced by bacterial plaque and/or by correcting the defects that lead to bone resorption. Nonetheless, in order to preserve the remaining dentition of patients with periodontitis, the disease has to be contained. Clinical intervention via non-surgical and/or surgical approach is necessary to re-establish healthy periodontal tissues.

Intervention in non-surgical periodontal therapy includes: oral hygiene and plaque control, scaling and root planning (SRP), maintenance and adjunctive use of Che mother a peutic agents. Periodontal phase 1 therapy may be sufficient to eliminate the signs and symptoms of mild periodontitis. Traditionally periodontal surgical procedure such as open flap debridement may results in tissue repair however, true regeneration of lost tissue is not achieved without the use of any regenerative approach.

The current techniques for regeneration encompass the utilization of a wide variety of surgical approaches: the use of bone grafting materials, barrier membranes,[6] the use of biologic modif

iers, other osteo conductive/ inductive materials or protein mixtures, exogenous growth factors, cell-based technologies, and genes from recombinant technology. According to the AAP Glossary of Periodontal Terms Periodontal regeneration involves a “reconstitution of the PDL along with new formation of alveolar bone and cementum”; in other words, it involves a return to the original, completely functional Perio dontium. Regeneration is a dynamic process that aims to recreate the tissues to their original structure and function. For periodontal regeneration to occur, formation of a functional epithelial seal, insertion of new connective tissue fibers into the root, reformation of a new acellular cementum on the tooth surface, and restoration of alveolar bone are required. The complexity in this treatment approach involves recruiting locally-derived progenitor cells that can differentiate into PDL cells, mineral-forming cement oblasts, or bone-forming osteoblasts.[7]

Although there are wide variety of agents are available which may be delivered locally or systemically as host modulating agent such as tetracycline, NSAID’s, statins, omega 3 fatty acids, anti-resorptive or bone sparing agent such as bisphosphonate. To overcome the adverse effect of bisphosphonate these agents were introduced with a target to achieve the periodontal tissue regeneration through bone formation when administered

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systemically. Currently there are "bone anabolic agents" or "bone forming agents" include teriparatide and sclerostin antibody. Teriparatide is commercially available with a name of "Forteo" which is a bioactive part of parathyroid hormone. It was the firstly approved by FDA in November 2002 for the treatment of osteoporosis like conditions especially in postmen opausal women. Teriparatide is a bio synthetic human parathyroid hormone which consists of 1-34 amino acid molecule of human PTH identical to the N-terminal portion of the hormone.[8]The chief cells of parathyroid gland secrete the parathormone which consists of a single chain of 84 amino acid. After the proteolytic cleavage of from pre-pro-parathyroid hormone (115 amino acids) to pro-parathyroid hormone (90 amino acids) it forms a mature hormone.[9]

PTH is an endogenous hormone with both anabolic (bone formation) and catabolic (bone remodelling) properties in bone. Animal experiments have docu mented an anabolic effect on both cancellous and cortical bone. Its application has been applied to the treatment of osteoporosis, although current research has focused on investigating PTH function in periodontal applications.[10] Bashutski et al. completed a randomized human clinical trial on 40 patients with intrabony defects who were supplemented with daily injections of 20mg PTH in conjunction with periodontal surgery. His results revealed that PTH had greater infrabony defect resolution, CAL gain, and PD reduction.[11]

Mechanism of action

Because PTH plays a role in the WNT/β-catenin signalling that downregulates sclerostin, which is an inhibitor of WNT - LRP5/ 6, and stimulates bone formation. Teriparatide is one of the targeted researched drugs among researchers with the aim of periodontal regeneration and bone formation. Teriparatide activates a signalling cascade that includes protein kinase-1, cyclic adenosine mono phosphate, and protein kinase. Both teriparatide and PTH have their biological activity through the specific G protein dependant pathway and cell surface receptors which are expressed on the osteoblast's cells and renal tubular cells. These two molecules bind with the surface receptor with the same affinity and potential and exerts the same physiological activity on alveolar bone and kidney. Furthermore, the activation of protein kinase -1, protein kinase-C, phospholipase C and cyclic adenosine monophosphate though the ligand binding molecules resulting in the increase in number of active osteoblasts cells and decrease the apoptotic activity of osteoblasts cells along with the new recruitment of bone lining cells especially newly formed osteoblasts cells.[12] Therefore, both teriparatide and parathyroid hormone represent the markers of the bone formation.

Growth factors such as Basic fibroblast growth factor 2 (bFGF-2) play role in exerting the anabolic effect of teriparatide. bFGF-2 regulates the proliferation and differentiation of osteoblast progenitor's cells and play an important role in the bone formation in response to teriparatide therapy.[13] Also, osteocytic Sclerostin (SOST) gene may be transcriptionally suppressed by PTH resulting in reduction of sclerostin molecule which could account for anabolic response to PTH.[14]

It is always a debateable question regarding the intermittent or continuous dosage of teriparatide and PTH dosage administration. However, the scientific literature accepted that the intermittent teriparatide is anabolic in nature while continuous dosage of endo genous PTH hormone is catabolic in nature. For proving this point there have been several mechanisms which were postulated. If intermittent dosage of PTH and continuous dosage of teriparatide is administered it may

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result in anabolic period where bone formation is stimulated by increasing the number of osteoblasts cells before a secondary increase in bone resorption. This time period is called a "anabolic window". If the dosage of PTH and teriparatide is administered vice versa it may result in persistent and markedly enhanced bone resorption and inhibit the bone formation because of increased the activation of nuclear factor kappa-B ligand (RANKL) and decrease in osteoprotegrin (OPG) expression.[15] The use of intermittent dosage of teriparatide may increase the thickness and connectivity in the trabecular bone usually seen in microcomputer tomography of trans iliac bone biopsies.

Table 1: pharmacokinetic properties of teriparatide

Bioavailability	95%
Route of administration	Subcutaneous through modified insulin pen, intravenously
Half life	75min, 10 mins after IV administration
Metabolism and route of eiimination	Liver and Kidney
Drug interaction	Clinically unproven
Dosage	20µg/day for 18 months in Europe and 24 months in US
Commercial availability	Forteo

Role of teriparatide on periodontal regeneration

Because of the anabolic property of teriparatide, it has a direct effect on the periodontal ligament cells and osteoblast cells. Scientific literature studies both in vivo and in vitro suggested that there is an increase in the proliferation and differentiation of osteoblast cells resulting in the bone formation more as compared to the bone resorption as seen his to logically and bio chemically. PTH and teriparatide both are the bio logical markers of the bone which may contribute in the treatment of Periodontitis. They act directly to stimulate bone formation, improve bone mass and quality, and reduce the osteoclastic activity. Teriparatide increase the trabecular and cortical bone micro structure indices.[16] Teriparatide exerts its action in bone formation in two aspects. Firstly, there is a direct stimulation of osteoblasts cells that are active during the remodelling process (remodelling-based bone formation) and the bone which was previously inactive (modelling-based bone formation). Secondly, there is an increase in the new Remo delling process. Both aspects may contribute in increasing the bone density when observed under the dual energy X- ray absorptiometry technology (non-invasive tool for the assessment of trabecular micro Archi tecture). Basically, remodelling and repair process undergo simultaneously for the maintenance of bony tissue in a healthier state and when teriparatide is stimulated there is a positive bone balance with in the remodelling process.

The primary goal of teriparatide administration is to enhance the healing process in periodontal regeneration as well as in various craniofacial defects. Also, there is a change in the bone mineral density after the administration of teriparatide. procollagen type-I N pro-peptide (PINP) which is an osteoblast derived protein and a diagnostic biomarker which may provide a supplemental information after the administration of teriparatide and reflect the changes in the bone mineral density similar to the other biochemical markers of bone resorption

The regeneration of periodontal ligament cells especially when the periodontium is damaged and is considered an important step for the success of periodontal regeneration in periodontal attachment apparatus. The periodontal ligament cells represent the heterogenous population of host progenitor cells that can be further

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differentiate into cement oblasts, osteoblasts, and fibro blasts. The certain proportion of periodontal ligament cells towards the alveolar bone are evidenced by the presence of bone markers such as alkaline phosphatase enzymes, osteopontin, and osteocalcin, bone-inductive factors, and the ability to mineralize their extracellular matrix in the presence of dexamethasone, ascorbic acid, and β-glycero phos phate. These unique property of Perio dontal ligament cells make a promising source to enhance periodontal regeneration.[17] The administration of teriparatide may increase the osteoblastic differentiation of periodontal ligament cells and the cellular ability to mineralize the extracellular matrix. Preliminary clinical studies have shown promising results with teriparatide for Perio dontal regeneration. The response of periodontal ligament cells is in the similar way as the osteoblast cells that can further show the presence of osteoblast markers gene expression.

Table 2: Outcome of various preclinical Human Studies of teriparatide in periodontal regeneration

Author, year	Administration route	Sample size: total (group)	Main outcome
Moore et al, 2010[18] Assessment of regional changes in skeletal metabolism following 3 and 18 months of teriparatide treatment.	Subcutaneous route	10 patients	The first study to show a direct metabolic effect of TPTD therapy on bone as measured by tracer kinetics at individual clinically important skeletal sites. Postmenopausal women with osteoporosis treated with TPTD had increased skeletal uptake of 99mTc-MDP, indicative of increased bone formation, which is supported by increases in bone turnover markers and BMD
Bashutski et al, 2010[11] Teriparatide and Osseous Regeneration in the Oral Cavity	Subcutaneous route	40 patients (20×2groups)	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. Teriparatide may offer therapeutic potential for localized bone defects in the jaw
Kuchler et al, 2011[19] Short-term teriparatide delivery and osseointegration: a clinical feasibility study.	Subcutaneous and oral route	24 patients (12×2groups)	The results provide the first histological data on the osseointegration of titanium study implants in individuals treated with teriparatide
Bashutski et al, 2012[20] Systemic Teriparatide Administration Promotes Osseous Regeneration of an Intrabony Defect: A Case Report.	Oral route	Case report	Teriparatide administration in conjunction with traditional open-flap debridement surgery offers potential for the treatment of severe intrabony defects resulting from chronic periodontitis

Table 3: Outcome of various preclinical Animal Studies of teriparatide in periodontal regeneration

Author, year	Administration route	Sample size: total (group)	Main outcome
And reassen et al,2004[21]	Subcutaneous	44 wistar rats	Rats treated with PTH (1-34) (60 µg/kg daily)

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Intermittent parathyroid hormone treatment enhances guided bone regeneration in rat calva rial bone defects.	route		showed increased tissue dry weight, ash content and concentration of the new tissue, and mechanical strength compared with vehicle-injected animals inside 5 mm diameter rat calva rial defects covered with membranes.
Jung et al, 2007[10] The effect of matrix bound parathyroid hormone on bone regeneration.	Local administration of PEG matrix containing matrix-PTH at an implant site	6 American Foxhounds (48 implants)	It is concluded that an RGD-modified PEG hydrogel containing PTH is an effective matrix system in obtaining bone regeneration.
Marqueset al, 2009[22] Parathyroid hormone administration may modulate periodontal tissue levels of IL-6, MMP-2 and mmp-9 in experimental periodontitis	Subcutaneous route	76 Wister rats (38×2 groups)	Periodontal tissue samples from rats with experimental periodontitis treated with PTH (1-34) (40 μg/kg daily) showed decreased MMP-9 activity, decreased level of interleukin-6 and of MMP-2, and a lower number of osteoclasts.
Yun et al,2010[23] Effect of systemic parathyroid hormone (1-34) and a β-tricalcium phosphate biomaterial on local bone formation in a critical-size ratcalvarial defect model	Subcutaneous route	100Sprague/Dawley rats (20×5 groups)	The histometric analysis showed that systemic PTH significantly enhanced local bone formation, bone fill averaging compared with PTH/β-TCP The PTH/β-TCP and β-TCP groups. Both showed limited biomaterials resorption.
Valderrama et al,2010[24] Evaluation of parathyroid hormone bound to a synthetic matrix for guided bone regeneration around dental implants: a his to morpho metric study in dogs	Local administration in hydrogel form	6 American Foxhounds	The effect of binding PTH covalently to a synthetic, RGD-modified PEG hydrogel marginally significantly improved bone formation at 2 weeks of healing as compared to PEG alone.
Staconvenet al, 2013[25] Effect of BMP-2, demineralized bone matrix and systemic parathyroid hormone (1-34) on local bone formation in a rat calvaria critical-size defect model calvaria critical-size defect model	Subcutaneous route	160 Sprague/Dawley rats	PTH (1-34) (15 μ g/kg daily) showed no meaningful additive effect on local bone formation in 8 mm diameter calva rial rat defects treated with DBM, ACS, rhBPM-2/ACS or left empty. The greatest bone formation was obtained with rhBPM-2/2/ACS or left empty. The greatest bone formation was obtained with rhBPM-2/
Iwai et al,2018 [26] Bone regeneration by freeze-dried composite of octa calcium phosphate	Local delivery as microparticles	30 wistar strain rats (5 ×6 groups)	The addition of teriparatide (1.0 or 0.1 μg) in disks composed by OCP or β-TCP and collagen significantly improved new bone formation in 9 mm

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collagen and teriparatide			diameter rat calva rial defects.
Park et al, 2019[27] Synergistic effect of hyperbaric oxygen therapy with PTH [1-34] on calva rial bone graft in irradiated rat	Subcutaneous route	24Sprague/Dawley rats (8×3 groups)	rhPTH (1–34) (30 µg/kg daily) alone, or in combination with HBO significantly increased bone formation in 5 mm diametercalvarial defects in rats that previously received localised radiation in that region. The new bone surface and residual material surface density of the PTH/HBO group was significantly higher than that of the control and PTH groups.

Adverse effects

Teriparatide have encountered both types of long term and short-term adverse effects. The Food and Drug Association categorized teriparatide as "Black box" warning because of increasing the cases of Osteosar coma especially encountered during animal studies. However, Osteosar coma have been reported as long-term complication after administration of teriparatide. These types of adverse effects may be dependent on the dosage (continuous or intermittent) as well as duration of the treatment. In 2010, one of the animal studies investigated that systemic administration of teriparatide ranges from 3-60 times more exposure in humans who were at the dosage of 20µg.[28]

It is contraindicated in hyper parathyroid, Paget's disease, osteosarcoma, patient's having medical history of skeletal disorders, pregnancy, lactation and any type of metastatic skeletal malignancy. However, clinical trials are going onto channelise the adverse drug effects in a more precise way.

Conclusion

Bone formation and remodelling is a complex continuous process involving many hormones. Bone volume reduction following tooth extractions and bone diseases such as period ontitis and osteoporosis causes serious problems and require a great understanding of the process. The discovery of teriparatide as a new anabolic agent opens a new door in the management of period ontitis. The administration of teriparatide as an adjunct in period ontal surgery or as a host modulating agent has widened the direction of period ontal treatment as well as in promotion of period ontal regeneration. As a newer anabolic agent teriparatide may have a multitude of differing effects, the safety and regimens of administration regarding dosing, location, and frequency need to be assessed and more studies and clinical trials are needed in terms of dental procedures. In future teriparatide may have a property of "double-edged sword" to enhance the therapeutic outcomes in terms of period ontal regeneration.

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