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TERIPARATIDE – A POTENTIAL BOON IN DENTISTRY

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ABSTRACT

Teriparatide, an effective anabolic agent is a recombinant form or a synthetic form of natural human parathyroid hormone. Though it is a drug usually indicated for the treatment of osteoporosis, it has promising application in various fields of dentistry. Its dosage based bimodal property on bone deposition and resorption can be utilised in periodontal surgeries, fracture healing, reconstructive surgeries, implant osseointegration and orthodontic tooth movement. This review highlights the possible applications of this novel drug in dentistry, its side effects, drug interaction and contraindications.

KEYWORDS: Osteoprotegerin, Parathyroid hormone related peptide (PTHrP), PTH (1-34), Synthetic parathyroid hormone, Teraparatide.

INTRODUCTION

Hormones are body's chemical messengers having diverse chemical structures produced by glands and are transported by the circulatory system to target distant organs to regulate physiology and behaviour. Humans have about 50 different known hormones that act on different aspects of bodily functions and processes out of which parathyroid hormone (PTH) or parathormone or parathyrin plays an important role.[1] Teriparatide is an effective osteo-anabolic agent which is a recombinant form of human parathyroid hormone (rhPTH).[2] The drug was approved by the Food and Drug Administration (FDA) on November 2002 for the treatment of osteoporosis in persons who are at high risk of having fracture as in postmenopausal women and in men with primary or hypogonadal osteoporosis. It contains first 34 amino acids of human PTH which is identical to the N-terminal portion of the hormone.[3] Parathormone is a single chain polypeptide of 84 aminoacids, which is

synthesised in and secreted by the chief cells of parathyroid glands. After two successive proteolytic cleavages from preproparathyroid hormone (115 aminoacids) to proparathyroid hormone (90 aminoacids) it forms a mature hormone.[4] Teriparatide is the generic name for all PTH (1–34) molecules. Another recombinant form which is available and approved in EU only is the full length PTH 1-84.[5]

PTH together with 1,25(OH)2 vitamin D, plays a key role in the phosphocalcic regulation and thus plays an vital role in the development of tooth and bone remodelling. It produces several distinct and independent effects on bone remodelling process, resulting in both bone formation (anabolic activity) and bone remodelling (catabolic activity). A continuous administration of PTH shows increase in the number of osteoclasts with enhanced osteoclastic activity, rapid turnover and decrease of bone mass where as an intermittent administration increases bone mass by stimulating osteoblast differentiation and prevention of its apoptosis.[6]

Studies on the structure and function of PTH have revealed that most of the biological activity of intact PTH (1–84) resides in the 1-34 N-terminal fragment of the hormone. It was found that a synthetic bovine PTH(1–34) was able to generate the major biological actions of the full-length native bovine PTH (1-84), including activation of adenylyl cyclase in bone and kidney cells, increased urinary excretion of cyclic adenosine monophosphate (cAMP) and phosphate in rats and elevation of blood calcium in rats, dogs and chickens.[7] Moreover, Teriparatide has a similar binding affinity for PTH receptor 1 as PTH (1–84).[8] PTH analogues have a rapid absorption rate after a subcutaneous injection with bioavailability of PTH 1–34 being 95% and PTH 1–84 being 55%. PTH 1–84 has a longer duration of action and the half-life after the injection for PTH 1–34 and PTH 1–84 is approximately 1 hour and 2.5 hours respectively.[9,10]

These facts, together with the practical difficulties in synthesizing large quantities of chemically pure PTH (1–84), led to the widespread use of recombinant PTH (1–34) as a surrogate for intact PTH in studies of hormone effect *in vitro* and *in vivo*. This review aims to update research on applications, benefits and adverse effects of the novel drug, teriparatide and its usage as a potential therapeutic agent in dentistry.

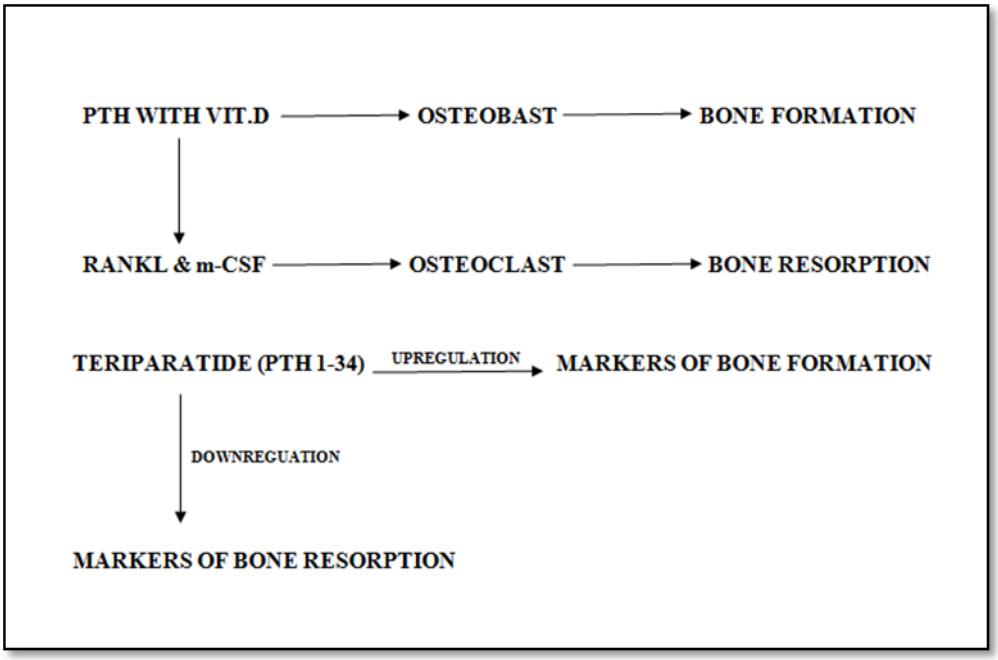
ROLE OF TERIPARATIDE ON BONE

Various in vivo and in vitro studies have proved distinct anabolic effects of intermittent PTH administration on bone.[11,12] The anabolic effect of intermittent PTH has also been extensively demonstrated in mice and rats.[13] Both full length PTH (1–84) and teriparatide (PTH 1–34) administration resulted in rapid up-regulation of markers of bone formation, but a down-regulation of markers of resorption.[14,15] Daily injections of PTH (1–84) or PTH (1–34) increase bone mass and reduce the incidence of fracture in postmenopausal women, in elderly men, and in women with glucocorticoid-induced osteoporosis.[6]

Deposition of bone is increased predominantly due to an increase in the number of osteoblasts, which is mediated by repeated delays of osteoblast apoptosis[16], enhancing the recruitment of preosteoblasts from marrow stromal cells and stimulating the maturation of lining cells.[6]

Intermittent PTH administration triggers the anti-apoptotic signalling pathways which involve cAMP mediated activation of protein kinase A (PKA), subsequent phosphorylation and inactivation of the pro-apoptotic protein Bad and increased transcription of anti-apoptotic like Bcl-2.[17] On the other hand, intermittent PTH also decreases the expression of histone H4 which is a marker of the cell cycle[18] and cell cycle inhibitors p27KIP1 and p21Cip1[19], in metaphyseal bone of young rats where replicating osteoblast progenitors is rich in number. This strongly suggests that intermittent exposure to PTH causes an exit of osteoblast progenitors from the cell cycle, which leads to the differentiation and suppression of proliferation of these cells.[6]

Continuous exposure causes increase in the osteoclast differentiating factor (ODF), also called as nuclear factor kappa ligand (RANKL) and decrease in the osteoprotegerin (OPG), a cytokine expressed by committed preosteoblastic cells. OPG binds to ODF and decreases the receptor activity (Table/Fig 1). Intermittent use has only transient effects on osteoclasts, thus net osteoblastogenesis takes place.[6]



Table/Fig. 1: PTH & Teriparatide role in bone remodelling.

Teriparatide initially promotes the formation of bone by rapidly increasing the markers of bone formation. Thereafter bone remodelling takes place where bone resorption predominates. This is associated with increase in bone resorption markers. The time period where actions of PTH are maximally anabolic is called as the "anabolic window".[5]

EFFECTS ON JAW BONES

Craniofacial bones are formed by intramembranous ossification and on the other hand long bones and vertebrae are formed by endochondral ossification. Since the developmental aspects of the two are different, mechanisms of PTH effect may vary according to their location.[3]

In cancellous bone as well as cortical bone, positive effects of teriparatide are seen on bone density, microarchitecture and geometry.[5,20] It stimulates apposition of periosteum leading to overall increase in cross-sectional area by increasing cortical area and thickness. The mechanical effect on inner one third of cortical bone is minimal where teriparatide increases the porosity and enhances bone microarchitecture and geometry.[5,21]

EFFECTS ON PERIODONTIUM

Numerous studies were conducted both *in vivo* and *vitro* to elucidate the role of PTH on PDL cells on the basis of anabolic properties of PTH established in osteoblasts and the fact that the

PDL cells show osteoblastic characteristics. These studies have suggested that periodontal ligament cells respond to PTH in a osteoblastic manner, both *in vitro*[22,23,24] as well as in *in vivo* models.[25]

PTH receptors were detected immunohistochemically in cementoblasts of rats.[26] In addition, studies have reported marked improvement of clinical and radiographic outcomes in patients with periodontal surgery in cases of severe, chronic periodontal disease and received daily injections (20 μg or placebo for 6 wks) of teriparatide. At 1 yr, the test group had significantly greater radiographic linear resolution of intrabony defects.[27,28] Thus, teriparatide therapy might also contribute in the treatment of periodontal diseases.

EFFECTS ON TOOTH ERUPTION

Parathyroid hormone related peptide **(**PTHrP) and PTH share significant sequence homology within the first 13 amino acid residues, which underlines the functional importance of the N-terminal residues in receptor signalling. However, the sequence homology decreases significantly in the 14–34 region, showing no recognizable similarity beyond residue 34.[29] For both PTH and PTHrP, the 15–34 region functions as the principal PTH1R binding domain.

PTHrP has a pivotal role in regulating embryonic development of the skeleton and other tissues via intracellular, paracrine and endocrine pathways.[30] It is widely expressed in cartilage, heart, kidney, hair follicles, placenta, breast, lungs and many epithelial tissues of foetus and normal adult.[31] PTHrP is secreted by the cells of the Reduced Enamel Epithelium where it acts as a signalling molecule to stimulate resorption of the bony crypt surrounding the tooth follicle. It is thus critical in intraosseous phase of tooth eruption. Type 1 PTH/ PTHrP receptor is found in the dental mesenchymal tissue adjacent to the teeth and in alveolar bone which suggest PTHrP to be a regulator of epithelial-mesenchymal interactions during development of tooth. PTH and PTHrP bind to parathyroid hormone/parathyroid hormone related peptide receptor (PTH1R) and exert osteo-anabolic effects.[32] Therefore, PTH and parathyroid gland extract enhance tooth eruption.[33]

PTHrP presumably promotes the osteoclastic resorption required for eruption of tooth by increasing the ratio of expression of RANK: OPG by cementoblasts. In study by Schipani et al in 1997, a lack of this receptor in mice models showed development of tooth bud with reduce in number of ameloblasts and disrupted odontoblastic layer and absence of

eruption.[31] There is a failure of tooth eruption in humans lacking the PTH/ PTHrP receptor as in Blomstrand chondrodysplasia.[34] Thus further studies on teriparatide can unravel the potential role of teriparatide in the treatment of tooth ankylosis.

EFFECTS ON TOOTH MOVEMENT

Orthodontic treatment, done to move poorly aligned teeth to a desirable position, has always been a lengthy process. The desire for shortening of the treatment period has lead to development of new methods for accelerating orthodontic tooth movement. The rate of orthodontic tooth movement is directly dependent on the rate of bone resorption occurring in the compressed periodontium in the direction of orthodontic force applied to the tooth. A study by Davidovitch et al. in the year 1972, revealed a threefold increase in number of osteoclasts and accelerated movement of upper right first molars on compression side with continuous administration of PTH on rat models by inserting an elastic band between the first and second molars.[35]

Root resorption is one of the major drawbacks of orthodontic treatment. Continuous infusion of PTH enhanced the removal of necrotic tissue from the site of bone resorption, thus preventing root resorption. Moreover, it also increased the amount of bone apposition on the tension side, thereby helping in stabilization and retention. Systemic continuous infusion of PTH (1-34) accelerated orthodontic tooth movement, but intermittent injection systemically did not increase the rate of tooth movement.[36] Although systemic continuous infusion did not have any adverse effect, yet continuous local infusion of PTH into the circumferential tissue around the teeth to be moved should be preferred. A slow release vehicle using methyl cellulose has been proved successful.[37]

Studies on rodent models have proved no significant impact on orthodontic tooth movement on intermittent administration of PTH. It stimulated bone apposition but had no effects on osteoclast-mediated bone resorption.[38,39] This property of intermittent administration can have added advantage when used selectively and can be exploited during the retention phase.[40]

A study done to evaluate morphologically the effect of teriparatide on induced orthodontic movement of the maxillary first molars in ovariectomized rats suggested that the treatment of osteoporosis with teriparatide is a good alternative for patients undergoing orthodontic treatment. Histologic sections obtained from the maxilla were prepared for the morphometric

analysis of dental movement, the thickness of the periodontal ligament and the number of osteoclasts in the pressure and tension areas of the apex of the root and alveolar crest in the distal root of the maxillary first molars.[41]

EFFECT ON FRACTURE HEALING

Clinical trials studies showed accelerated fracture-healing in pelvic with PTH[42] and distal radial fractures.[43] When treated with systemically administrated PTH the volume, quality, and mechanical strength of the callus are increased. PTH enhanced early healing of closed fractures in long bones[44,45] and mandibular fractures in ovariectomized rats.[46]

A shorter healing time and an early improved callus formation with once daily injection of 20 μg or 40 μg teriparatide was obtained in post-menopausal women who had sustained distal radial fractures.[43] Successful use of teriparatide in cases associated with non union of sternal fractures and atrophic femur shaft fracture have been reported.[47,48] Thus these studies highlight the therapeutic potential of teriparatide in fracture healing.

EFFECTS ON IMPLANT THERAPY

Dental implants have become a popular and effective way to replace missing teeth. Successful osseointegration is the key to implant success and highly depends on adjacent bone. PTH in combination with guided bone regeneration and bone grafts could enhance alveolar bone formation in animals.[49,50,51,52] Moreover, alveolar bone has a better response to PTH than other parts of the mandible and maxilla.[53] Intermittent PTH prevents further bone loss and fastens new bone formation.[54,55]

Subcutaneous administration of 30 μg/Kg of rhPTH(1-34) intermittently thrice a week after placement of titanium implants in proximal metaphysic increased cancellous bone density around the implant and also increased the degree of contact between the implants and bone.[56] Improved initial fixation of implants and high bone implant sheer strength was seen using intermittent PTH in osteoporotic rats with hydroxyappatite-coated implants.[57] Intricately fused PTH with various biomaterials like poyethylene gycol with the help of tissue engineering is now available. This enhances bone generation and implant osseo-integration.

EFFECT ON RECONSTRUCTIVE SURGERIES

Reconstructive surgeries of critical-sized defects remain a challenge to surgeons. To investigate adjunctive effect of PTH on the healing of devitalized allografts in critical femoral

defects, animal studies have been designed. A better healing result, significantly enhanced callus formation and graft-host integration, along with 2-fold increase in normalized callus volume and higher mechanical strength of the graft-host junction was seen at 6 wks.[58,59] Based on these studies, further investigation of the effect of PTH on large defects are required. Higher mineralized tissue volume, mineral content and bending strength was found after distraction osteogenesis on treatment with PTH in rabbits.[60]

Osteotomy of one or both jaws is done to correct jaw relationships, followed by repositioning the jaws to acquire ideal alignment and fixation. If stabilization between the gaps of bone segments could be faster, post-operative discomfort from temporary immobilization of the jaw would be greatly reduced. The role of PTH in reducing healing time might prove beneficial to patients undergoing orthognathic surgeries. A radiographic union of 1 mm surgical defect was achieved with greater radiographic intensity, larger callus areas, and greater stiffness in PTHrP-treated group at 6 wks, compared to 20% in the control group in ulnae of rabbits.[45]

ROLE IN OSTEONECROSIS OF JAW

Long term use of bisphosphonate can cause necrosis, exposed bone in the jaw, pain, swelling, and various dysesthesias known as Osteonecrosis of jaw (ONJ). Though the mechanism is unclear, poor oral hygiene, traumatic dental procedures, old age, neoplasms like multiple myeloma and usage of steroid can pose as risk factors. The duration of bisphosphonate also plays a vital role. Bisphosphonates inhibit osteoclastic activity causing anti-resorptive action and continue to localize on bone for a long duration owing to its longer half life. Teripeptide reduces microdamage accumulation in the bone and increases bone remodelling by promoting osteoblastic differentiation. It may also help in removal of necrotic bone and accelerate healing. Although the mode of treatment of ONJ is symptomatic, teriparatide can be used as an adjunct.[5]

ADVERSE EFFECTS

Both short term and long term side effects have been encountered. An increased continuous teriparatide administration can cause deleterious effects on skeletal, gastrointestinal, neural system. Weakness, fatigue, bone pain, myalgia, osteoporosis, loss of appetite, nausea, vomiting, constipation, polyuria, polydipsia, cognitive impairment.[40]

It is absolutely contraindicated in primary and tertiary hyperparathyroidism, pre-existing hypercalcemia, Paget's disease, osteosarcoma, persons with history of other skeletal disorders, open epiphysis in children, pregnancy, lactation, end-organ failure, elevated alkaline phosphatise of uncertain cause, metastatic skeletal malignancy and prior skeletal irradiation. Teriparatide when co-administered with drugs like digoxin in high doses (>5mg/day) or intravenous furosemide can cause hypercalcemia and hypercalciuria for a transient period.[5,40]

Osteosarcoma has been reported to be a long term complication of teriparatide use. The incidence of osteosarcoma is 1 in 250,000. Although the incidence in teriparatide users is not yet known, Harper at al., reported the first case in 2008.[10]

CONCLUSION

Teriparatide, widely known for its use as an osteoporosis therapeutic, has the potential to stimulate bone deposition in comparison to bisphosphonates and calcitonin which inhibits bone resorption rather than ability of bone apposition. Its effect is both time and dose dependent. A continuous administration of teriparatide has an adverse effect on bones, where as an intermittent exposure in optimum doses leads to an increase in the number and activity of osteoblasts improving bone mass and skeletal architecture. This dual property of teriparatide can be exploited in the field of dentistry to improve dental therapeutic outcomes in periodontal surgeries, implant integration and orthodontic stability. Based on the favourable pre-clinical outcomes, further human clinical trials on various dental procedures and its safety aspects should be investigated. A local targeted drug delivery system of the drug should be developed which will not have effect on the other non targeted areas and also avoid systemic complications.

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