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Effects of teriparatide on the osseointegration of dental implants: a literature review of animal studies

Kyeong-Soo Ko, Byung-Kyu So, Eui-Seok Lee, Ho-Kyung Lim

Department of Oral & Maxillofacial Surgery, Korea University Guro Hospital, Seoul, Korea

Dental implant is one of the most effective methods for restoring missing teeth. Osseointegration, which is influenced by various factors including bone quality around the implant fixture, is important to achieve successful implantation. We investigated the relationship between osseointegration and teriparatide, which has been recently used as an alternative to bisphosphonate, in animal studies. A total of 10 studies were selected upon conducting a thorough search using the keywords '(parathyroid OR teriparatide) AND dental implants AND osseointegration' in PubMed/Medline databases. In these studies, various indicators, such as stability and fixation torque of implants, density of peri-implant bone, and formation of new peri-implant bone according to the administration of teriparatide were investigated. Since it was found that the administration of teriparatide had a positive effect on osseointegration in most animal studies, we would like to report the findings obtained through a literature review. **(THE JOURNAL OF KOREAN ACADEMY OF OSSEOINTEGRATION 2021;13(1):42-48)**

Key words: Teriparatide, Osseointegration, Dental implant, Animal study

INTRODUCTION

Dental implant is one of the most effective method for restoring missing teeth[1]. Although the success and survival rates of these implants are increasing with the development of materials and technologies, implant failure is a major burden for clinicians[1]. For a successful implant, sufficient primary stability must be obtained, which may be achieved by ensuring that the implant is firmly fixed to the bone[1]. Osseointegration is affected by various factors, such as surface and design of the implant fixture, density and quality of bone, and systemic diseases such as diabetes and other clinically relevant factors such as smoking[2-6].

Osteoporosis is a metabolic disease wherein the mass of bone per unit volume decreases as bone density decreases[7]. Patients with osteoporosis are at risk of bone fractures in various parts of the body, such as the spine and pelvis, and bisphosphonates are used as the primary treatment drugs to prevent these complications[8,9]. Bisphosphonates reduce bone resorption by limiting the function of osteoclasts, thereby effectively preventing fractures in osteoporotic patients[8,9]. However, medication-related osteonecrosis of the jaw (MRONJ) may occur when invasive treatment of the oral and maxillofacial region is performed in patients taking bisphosphonates[8]. Therefore, the need for a drug that can replace bisphosphonates has emerged, and teriparatide has recently been gaining attention[9]. Teriparatide is a recombinant human parathyroid hormone (rhPTH)[9], which, unlike bisphosphonates, induces the differentiation of osteoblasts, stimulates existing osteoblasts to form a new bone, and reduces apoptosis of osteoblasts[9]. Moreover, its fracture-preventing effect is as effective as that of bisphosphonates and is known to increase bone mineral density (BMD)[9].

Currently, the relationship between bisphosphonates and dental implants is relatively researched[10,11]. It has been reported that when bisphosphonates were used locally, there are positive effects on implant osseointegration, such as better stability, less peri-implant bone loss, high implant survival rate, and no toxicity[10]. However, the relationship between systemic administration of bisphosphonates and osseointegration remains controversial[11]. In studies using bisphosphonates systemically in an patients with osteoporosis, bone-to-implant contact (BIC) was higher in the group administered with bisphosphonates; however, the results were not significant[11].

Although many comparative studies have been conducted on bisphosphonates, research on the relationship between teriparatide and osseointegration of implants is currently in progress.

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Corresponding Author: Ho-Kyung Lim, Department of Oral & Maxillofacial Surgery, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea, Tel: +82-2-2626-3272, Fax: +82-2-837-6245, E-mail: ungassi@naver.com

Therefore, this study aimed to summarize the latest knowledge on the relationship between teriparatide and osseointegration through a review of animal studies.

MATERIALS AND METHODS

1. Search strategy

The search terms '(parathyroid OR teriparatide) AND dental implants AND osseointegration' were searched on the databases of PubMed/Medline until September 2021, and a total of 32 studies were obtained. Among these, we excluded the following: review articles and non-English studies, as well as studies not conducted on animals, focused on systemic diseases other than osteoporosis, implemented bone grafting, and those that were not related to osseointegration. As a result, 10 studies remained, half of which induced osteoporosis, while the other half did not.

2. Data extraction

In each study, we extracted the following information: author(s), year of publication, type and number of animals, method for inducing osteoporosis, type of parathyroid hormone (PTH), control group, type and system of the implant, observation period, method for ensuring osseointegration, and research results.

RESULTS

The results of studies conducted with osteoporosis induction in animals are summarized in Table 1, and those conducted without osteoporosis induction are summarized in Table 2.

Three out of 10 studies used New Zealand white rabbits[11-13], and two studies used Sprague-Dawley rats[14,15]. The remaining studies used Wistar rats[16-20]. The number of animals used in the study varied from 14 to 45[12-21]. The diameter and length of the implants used ranged from 1 mm to 3.8 mm and from 3 mm to 13 mm, respectively[12-21]. The postoperative observation period varied from 1 week to 60 days[12-21]. For teriparatide, rhPTH was used in all 10 studies (Forteo-Eli Lilly, Indianapolis, IN, USA 12,15,17; hPTH [1-34], Peptide Institute, Osaka, Japan[16]; 1-34 synthetic PTH, R&D Systems Inc., Minneapolis, MN[14]; Forsteo®; Eli Lilly, Houten, the Netherlands[13]; pTH [1-34], BACHEM, Bubendorf, Switzerland[18]; PTH, Sigma, St. Louis, MI, USA[20]; Forteo, Eli Lilly do Brasil Ltda, São Paulo, Brazil[21]). In the five studies that induced osteoporosis, one study performed orchiectomy[17], and the rest performed ovariectomy[12-14,16]. In all studies that did not induce osteoporosis, saline or placebo was administered to the control group[15,18-21], whereas in studies that induced osteoporosis, saline[12,13,16], bisphosphonates[16], and placebo were used as controls[13,14,17].

As a radiological analysis index, five studies investigated the peri-implant bone volume per tissue volume (BV/TV), and these studies showed that the BV/TV value significantly increased in the PTH-administered group[12,15-17,20]. Two studies investigated peri-implant trabecular thickness (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp), which showed significantly higher values of Tb.Th when PTH was administered[15,17].

For histological analysis, six studies investigated BIC, all of which showed that when PTH was administered, the BIC value was significantly increased compared to the control group[13,15-17,19,20]. Two studies have investigated the bone turnover rate around implants[14,17]. As a result, when PTH was administered, both the bone turnover rate and generation of new bone were significantly higher[14,17]. Mafra et al. investigated the bone filling (BF) within the implant threads and peri-implant proportion of mineralized tissue (PMT), including BIC[19]. It has been reported that the values of BF and PMT in the dense bone regions were significantly higher in the group treated with PTH than in the controls[19]. In a study by Uchida et al., the ratio of peri-implant bone, density of osteoblasts, number of osteoclasts, and ratio of collagen were investigated through histological examination[18]. In the group administered with PTH, a significant increase was observed in the number of osteoclasts, osteoblasts, osteocytes around the implants, ratio of bone inside the implant thread, and amount of collagen[18].

In addition, one study investigated the implant stability quotient (ISQ) and two other studies investigated the removal torque to confirm the stability and osseointegration of the implant[12,16,21]. All of these studies reported that the ISQ or removal torque significantly increased when PTH was administered[12,16,21]. Two studies investigated the peri-implant BMD, and both of them reported a significant increase in peri-implant BMD when PTH was administered[13,15].

DISCUSSION

Osseointegration is the structural and functional direct bonding between the bone and the implant surface microscopically[22,23].

Table 1. Studies on the relationship between teriparatide and osseointegration after osteoporosis induction in animals

Author and year	Animals	Method for inducing osteoporosis	Sample size	PTH	Control group	Implant system	Observation period	Parameters	Results
Yoshifumi Oki et al. 2017	New Zealand white rabbits	Ovariectomy	15	Subcutaneous PTH (Forteo–Eli Lilly, Indianapolis, IN, USA)	Saline	Titanium implants (diameter, 3.8 mm; length, 6.5mm) (SETiO®, GC, Itabashi–ku, Tokyo, Japan)	4 weeks	ISQ total bone ratio	The ISQ values of the PTH groups were signifi–cantly higher than those of the control group ($P < 0.05$) The bone was thicker and more trabecular around the implant sockets in the PTH specimens than in the control specimens. The bone area around the implant socket was significantly greater in the PTH group than in the control group ($P < 0.05$).
Aya Shibamoto et al. 2018	Wistar rats	Ovariectomy	44	Subcutaneous PTH (hPTH [1–34]; Peptide Institute, Osaka, Japan)	Saline Alendronate	Titanium implant (diameter, 2.0 mm; length, 13 mm) (cp–Titanium Grade 2, machine surface)	4 weeks	Removal torque test BIC BV/TV	PTH administration significantly increased the biomechanical strength of the implant – bone interface compared with the saline–treated ($P < 0.01$). BIC was significantly increased by PTH admin–istration ($P < 0.01$) BV/TV were significantly enhanced by PTH administration ($P < 0.01$)
P. H. S. Gomes–Ferreira et al. 2020	Wistar rats	Orchiectomy	24	Subcutaneous PTH (Forteo–Eli Lilly, Indianapolis, IN, USA)	Orchiectomized Sham control	Titanium implant (diameter, 1.5 mm; length, 3.5 mm) (Neodent®, Curitiba, Paraná, Brazil)	60 days	BV/TV Tb.Th Tb.N Tb.Sp BIC MAR NBA	The experimental group revealed statistically significant higher values for BV/TV, Tb.Th, and BIC parameters than those of the orchiectomized group ($P < 0.05$) In the bone turnover analysis (MAR, NBA), the experimental group presented the highest results followed by the sham surgery and orchiectomized groups ($P < 0.05$)
Hyun–A Heo et al. 2015	Sprague–Dawley rats	Ovariectomy	27	PTH (1–34 synthetic PTH R&D Systems Inc., Minneapolis, MN)	Ovariectomized Sham control	Titanium implant (diameter, 1.2 mm length, 3.0 mm) (Ti–Al–V; Leibinger Stryker, Freiburg, Germany)	1, 2, 4 weeks	New bone on the implant surface	The amount of newly formed bone around implants in the PTH group was comparable to that of the control group. Ovariectomized group displayed relatively small amount of new bone.
M. Isabel Almagro et al. 2012	New Zealand white rabbits	Ovariectomy	38	PTH (Forsteo®; Eli Lilly, Houten, the Netherlands)	Healthy Saline (Ovariectomized)	Titanium implants (diameter, 2.5 mm; length, 7.0 mm) (Branemark System® with Ti UniteTM Surface Dental Implants; Nobel Biocare AB, Göteborg, Sweden)	6, 20 weeks	Peri–implant BMD BIC	PTH increased BIC compared with control rabbits ($P < 0.005$). PTH–induced new bone formation around external and internal surfaces of titanium implants led to a significantly increased BMD at the peri–implant area in osteoporotic rabbits compared with vehicle ($P < 0.005$).

PTH, parathyroid hormone; rhPTH, recombinant human parathyroid hormone; ISQ, implant stability quotient; BIC, bone–to–implant contact; BV/TV, bone volume per tissue volume; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; MAR, mineral apposition rate; NBA, neoformed bone area; BMD, bone mineral density.

Table 2. Studies on the relationship between teriparatide and osseointegration without inducing osteoporosis in animals

Author and year	Animals	Sample size	PTH	Control group	Implant system	Observation period	Parameters	Results
Yusuke Uchida et al. 2020	Wistar rats	14	human PTH (pTH [1–34], BACHEM, Bubendorf, Switzerland)	Saline	Titanium implant (diameter, 2.0 mm; length, 3.5 mm) (Kyocera Co. Ltd., Kyoto, Japan)	5 weeks	BAF Osteocyte density N.Oc/BS CAF Type I collagen Type III collagen	PTH significantly increased the number of osteoblasts, osteocytes, and osteoclasts in the total inside and outside areas of all implant threads PTH significantly increased bone area and the amount of collagen within the total inside areas of all implant threads
Liting Jiang et al. 2018	Sprague–Dawley rats	36	subcutaneous PTH (Forteo® by Eli Lilly Company, Indianapolis, USA)	Saline	Titanium implant (diameter, 2.0 mm; length, 8.0 mm)	5 weeks	BMD BV/TV Tb.Th Tb.N Tb.Sp BIC	PTH group presented significantly increased in BMD, BV/TV, and Tb.Th around the peri–implant region compared to controls ($P < 0.05$). PTH group presented significantly increased BIC ($P < 0.05$) when compared to controls. Vascular volume fraction increased significantly in the PTH group ($P < 0.01$)
Carlos Eduardo Secco Mafra et al. 2019	Wistar rats	45	subcutaneous PTH [1–34]	Saline	Titanium implant (diameter, 2.2 mm; length, 4.5 mm)	30 days	BIC BF PMT	PTH groups presented significantly higher values of BIC in the cortical region than that of the control group ($P < 0.05$). PMT in the cortical region and concentrations of PTH positively influenced bone density when compared to the control group ($P < 0.05$). In the cancellous bone, no differences between groups were observed ($P > 0.05$). PTH groups presented significantly higher BF value in the cortical region than that of the control group ($P < 0.05$).
Marcelo Soeiro Corsini et al. 2008	New Zealand white rabbits	20	rhPTH [1 - 34] (Forteo, Eli Lilly do Brasil Ltda, São Paulo, Brazil)	Placebo	Titanium implant (diameter, 3.75 mm; length, 8.0 mm) (ACE, Surgical Supply, Brockton, Mass)	4, 8 weeks	Removal torque test	The mean removal torque values at 28 days were 37.0 ± 4.36 Ncm and 47.4 ± 6.77 Ncm for the control and test groups, respectively ($P < 0.05$). The mean removal torque values at 56 days were 45.8 ± 3.96 Ncm and 55.8 ± 2.86 Ncm for the control and test groups, respectively ($P < 0.05$). Removal torque was significantly higher in the test groups than that in the control groups ($P < 0.05$).
Birgit Mair et al. 2009	Wistar rats	20	rhPTH [1–34] (PTH, Sigma, St. Louis, MI, USA)	Vehicle injection	Titanium implant (diameter, 1.0 mm; length, 3.0 mm)	4 weeks	BIC BV/TV	PTH groups represent significantly higher BV/TV and BIC value in the medullary compartment than that of the control groups ($P < 0.05$).

PTH, parathyroid hormone; rhPTH, recombinant human parathyroid hormone; BAF, bone area fraction around implants; N. Oc, BS, number of osteoclasts per bone perimeter in each area of interest; CAF, collagen area fraction; BMD, bone mineral density; BV/TV, bone volume per tissue volume; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; BIC, bone–to–implant contact; BF, bone filling within the implant threads; PMT, proportion of mineralized tissue.

Generally, it means that a functioning implant is firmly fixed without mobility and clinical problems[22,23]. Several factors influence osseointegration, such as the material, surface, design of the implant, surrounding bone density, and bone quality[2,23]. In addition, steroids, radiation exposure history, and metabolic diseases such as liver disease and diabetes, could affect osseointegration[3-5,23].

Osteoporosis is a bone disorder that increases the risk of fracture by decreasing bone density and quality[24]; the unbalanced bone turnover rate can affect bone strength[24]. Normally, the bone resorption action of osteoclasts and the osteogenic action of osteoblasts are balanced, thereby obtaining sufficient strength to resist fracture[24]. However, especially in postmenopausal women, estrogen is deficient[24]. Reduced estrogen levels prolong the lifespan of osteoclasts and shorten that of osteoblasts, thereby increasing bone resorption and reducing bone formation[24]. Moreover, postmenopausal women have a higher risk of osteoporosis due to lower bone mass[24]. In the early 1990s, hormone therapy using conjugated equine estrogens and medroxyprogesterone acetate was attempted as a treatment for osteoporosis[25]. Although hormone therapy certainly reduces the risk of fractures due to osteoporosis, it has disadvantages in that it increases the risk of cardiovascular or cerebrovascular disease and breast cancer[25].

Therefore, pharmacological treatment of osteoporosis focuses on reducing bone resorption and increasing bone formation[26]. Bisphosphonates are used as the first option, and it restrict osteoclasts to reduce bone resorption and prevent fractures due to osteoporosis[8,9,27]. However, recently, issues regarding MRONJ brought about by bisphosphonates have been raised[28]. According to the American Association of Oral and Maxillofacial Surgeons, MRONJ is defined when a bone has been exposed for more than 8 weeks, and the patient has previously taken a bone resorption or an angiogenesis inhibitor, without history of irradiation or metastatic lesions in the maxilla[29]. If bisphosphonates are taken within 4 years, dental procedures can be performed relatively safely for MRONJ[29,30]. However, as bisphosphonates are administered for a long period of time, formulations with a long half-life are continuously accumulated in the body, thereby increasing the risk of MRONJ[29,30].

Considering the abovementioned reasons, a drug that has recently gained attention is teriparatide. Currently, it is administered instead of bisphosphonate to prevent fractures that may occur during drug holidays after long-term bisphosphonate use or to prevent MRONJ in patients with severe osteoporosis[30]. Teriparatide is an rhPTH; hence, unlike bisphosphonates, it does not inhibit bone resorption but improves bone quality and bone mass by stimulating osteoblastic action of osteoblasts[26]. Teriparatide also increases the activity of osteoclasts, but because the activity of osteoblasts is increased beyond normal, the rate of bone turnover increases, and overall bone mass and quality are improved[31].

However, temporary side effects, such as pain and swelling at the injection site, nausea, headache, leg cramps, and dizziness may occur even when teriparatide is administered[32]. A previous study showed that long-term continuous administration of teriparatide at a dose of 75 mg/kg/day in rats is associated with the development of osteosarcoma[30,32]. Therefore, the Food and Drug Administration discourages the continuous administration of teriparatide for more than 2 years. Moreover, it is contraindicated to those with a high risk of osteosarcoma (e.g. patients with Paget's disease)[30,32].

In this study, the relationship between teriparatide and osseointegration was investigated using animal studies. PTH was administered to the animals used in the study, and various methods were employed to check the stability and fixation of the implant, ratio of bone around the implant, density, and contact[12-21]. In addition, the formation of a new bone around the implant has been investigated[12-21]. Based on the study results, it was observed that the abovementioned indicators significantly increased in the group administered with PTH compared to the group not administered with PTH[12-21]. Although it was an animal study, it could be expected that the administration of PTH had a positive effect on the osseointegration of the implant and bone[12-21].

To date, the study by Kuchler et al. is the only human study that could be obtained by searching PubMed/Medline databases. They conducted a study on 24 patients with edentulous mandible[33]. Originally, four implants were placed in the mandibular interforaminal area, and another two (length, 4 mm; width, 2 mm) were placed during their study[33]. Of these, 12 patients self-administered 20 μg of teriparatide daily, and the others did not[33]. Nine weeks after implantation, the study implant was removed during the second operation, and BV/TV and BIC were investigated, but no significant difference was observed between the experimental and control groups[33].

This study reviewed various animal experiments and found that the clinical use of PTH had a positive effect on the osseointegration of implants[12-21]. However, animal studies cannot quantify

the side effects of PTH administration, such as pain and swelling, nausea, headache, leg cramps, and dizziness[30,32]. In addition, since fatal side effects such as osteosarcoma may occur depending on the PTH dose, more studies are needed in the future to determine the effectiveness of PTH for the purpose of increasing osseointegration in humans[30,32].

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