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REVIEW

Efficacy of parathyroid hormone supplementation on the osseointegration of implants: a systematic review

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Abstract
Objective The aim of the present systematic review was to assess the efficacy of parathyroid hormone supplementation on the osseointegration of implants.
Methods The addressed focused question was *Does parathyroid hormone supplementation affect osseointegration around implants?* Indexed databases were searched from 1965 up to and including April 2015 using various key words including: *Bone to implant contact*; *implant*; *parathyroid hormone*; and *osseointegration*. Letters to the Editor, case-reports/case-series, historic reviews, commentaries and articles published in languages other than English were excluded. The pattern of the present systematic review was customized to primarily summarize the pertinent data.
Results Eighteen studies fulfilled the eligibility criteria. Evidence was limited to preclinical animal studies only (11 studies in rodents, 4 in dogs and 3 in rabbits). Number of titanium implants placed ranged between 20 and 80 implants. Results from 16 studies showed that PTH supplementation enhanced new bone formation and/or BIC around implants. One study suggests that PTH-coated implants improve BIC and BA. One study showed no significant difference in BIC and new bone formation around implants with PTH hydrogel placement.
Conclusion Efficacy of PTH supplementation on osseointegration of implants shows promising results in animal models, however further investigation is necessary to assess the effectiveness in humans.

Keywords Bone to implant contact · Implant · Osseointegration · Parathyroid hormone

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Introduction

The parathyroid hormone (PTH) plays an essential role in the maintenance of calcium homeostasis through its actions in the regulation of bone remodeling [1]. PTH induces bone formation by downregulating the expression of sclerostin (a protein that inhibits bone formation) in osteocytes thereby permitting the anabolic signaling pathways to proceed [1]. Continuous exposure to PTH induces bone loss mainly due to upregulation of the receptor activator of nuclear factor kappa-B ligand (RANKL) expression and inhibition of osteoprotegerin expression [2]; whereas intermittent, low doses of PTH result in osteoanabolic effects [3]. In an experimental study on 2-year-old rats, Ejersted et al. [4] investigated the effect of intermittent PTH therapy on vertebral bone. The results were based on biomechanical and histomorphometric analysis of vertebral bone with and without (control) PTH therapy. The results showed nearly doubling of the cancellous bone volume and trabecular bone thickness after PTH treatment as compared to controls. Moreover, in contrast to the control group, PTH

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therapy also induced a considerable increase in the strength of the vertebral body [4]. Similar results have been reported in other preclinical studies [5, 6].

Early osseointegration and primary stability are parameters that play a role in the long-term survival and success of implants [7–10]. It has been hypothesized that PTH activates resting lining cells to initial de novo bone formation [11]. Considering these actions of PTH, it has been proposed that PTH may be a potential treatment for bone loss around implants. In an experimental study, Daugaard et al. [12] assessed the effect of systemic intermittent PTH treatment (5 μg/kg/day) on the cancellous osseointegration of unloaded implants inserted press-fit in intact bone of dogs. In this study, osseointegration was assessed using histomorphometry and fixation by push-out test to failure. The results showed that intermittent PTH supplementation improved histological osseointegration of a prosthesis inserted press-fit at surgery in cancellous bone [12]. Similar results were reported by Corsini et al. [13] and Mair et al. [14]. However, controversial results have also been reported regarding the efficacy of PTH supplementation with reference to its effects on osseointegration. Kuchler et al. [15] investigated the effect of intermittent PTH supplementation on osseointegration of implants placed in the tibiae of 6-month-old female Wistar rats with or without streptozotocin (STZ) induced diabetes. In this study, the rats received subcutaneous injections of PTH (60 μg/kg) or a placebo starting at the day of implant insertion into the tibia. The results demonstrated that intermittent PTH supplementation is ineffective in prompting osseointegration in animals with STZ-induced diabetes [15]. Likewise, Valderamma et al. [16] reported no significant influence of PTH supplementation on the osseointegration of implants placed in rats with STZ-induced diabetes.

There seems to be a relationship between intermittent PTH supplementation and osseointegration of implants. However, due to the controversial results reported in this regard, the authors of the present study decided to systemically review indexed literature in an attempt to clarify the association between PTH supplementation and osseointegration. Therefore, the aim of the present study was to systematically review the efficacy of PTH supplementation on the osseointegration of implants.

Material and methods

Focused question

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed. The addressed focused question was *Does PTH hormone supplementation influence osseointegration around implants?*

Eligibility criteria

The eligibility criteria were as follows: (a) original studies (clinical and experimental); (b) inclusion of a control group (osseointegration around implants without PTH supplementation); and (c) intervention: effect of PTH supplementation on osseointegration. Letters to the Editor, historic reviews, commentaries, case-series and case-reports were excluded.

Literature search protocol

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE, Scopus, Web of knowledge and Google-Scholar databases were searched from 1965 up to and including March 2015 using different combinations of the following key words: *Bone to implant contact*; *implant*; *Parathyroid hormone*; and *osseointegration*. Titles and abstracts of studies identified using the above-described protocol were screened by two authors (FJ and SVK) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Hand searching and cross checking of the reference lists of potentially relevant original and review articles were also performed to identify any studies that could have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors (Fig. 1). The Cohen's kappa score for the inter-examiner reliability was 1. The pattern of the present systematic review was customized to mainly summarize the relevant data.

The initial search yielded 30 studies. Twelve studies which did not fulfill the eligibility criteria were excluded (see Appendix). In total, 18 experimental studies were included and processed for data extraction.

Quality assessment

Quality Assessment of studies that were included was performed in an attempt to increase the strength of the present systematic review. The 18 studies that were included underwent a quality assessment with the Critical Appraisal Skills Program (CASP) Cohort Study Checklist [17]. The CASP tool uses a systematic approach based on 12 specific criteria, which are: (1) Study issue is clearly focused; (2) Cohort is recruited in an acceptable way; (3) Exposure (PTH delivery) is accurately measured; (4) Outcome (osseointegration and/or new bone formation around implants) is accurately measured. (5) Confounding factors are addressed; (6) Follow-up is long and complete; (7) Results are clear; (8) Results are precise; (9) Results are credible; (10) Results can be applied to the local population; (11) Results fit with available evidence; and (12) There are important clinical implications. Each criterion was given a response of

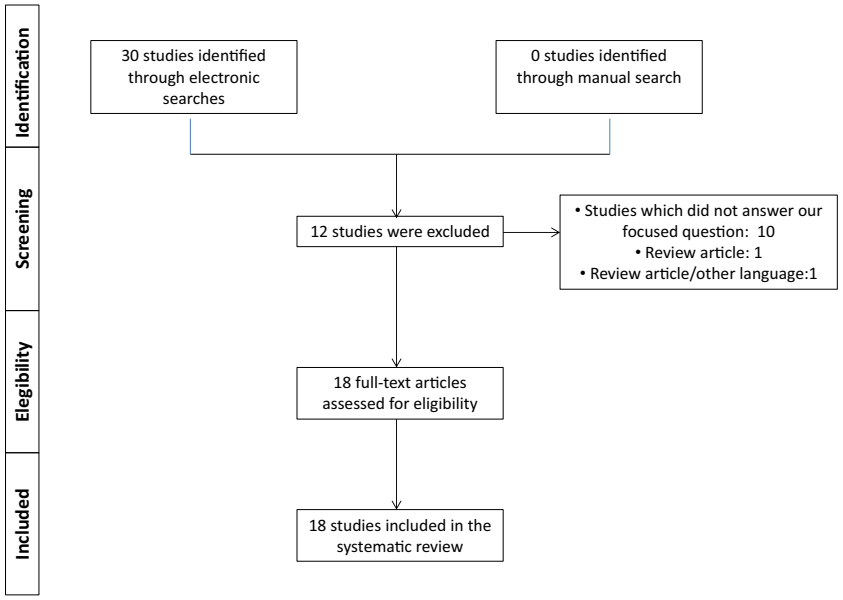

Fig. 1 Article selection flow chart for the systematic review according to PRISMA guidelines

either *Yes*, *No*, or *cannot tell*. Each study could have a maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Results

General characteristics of the studies included

In total, 18 studies [12–16, 18–30] were included. All studies [12–16, 18–30] were prospective and were performed in vivo. Three studies [13, 18, 23] were performed in rabbits; eleven studies [14, 15, 18, 21, 22, 24–30] were performed in rodents, and male dogs were used as study subjects in four studies [12, 16, 19, 20]. Six studies [14, 15, 21, 22, 26–28] were performed in female rodents, two studies [24, 25, 29] were performed in male rats, and one study [30] performed in mice did not specify the gender of animals used. In two studies [13, 23] male rabbits were used as study subjects and one study [18] was performed in female rabbits. In all studies [12–16, 18–30], the follow-up period ranged between 2 and 12 weeks. In six studies [12–14, 19, 20, 29] subjects in the test group received PTH therapy whereas animals in the control group did not. Lima et al. [27] evaluated the effects of PTH on osseointegration in rats exposed to cigarette smoke inhalation (CSI). In the study by Almagro et al. [18], effectiveness of PTH on implants osseointegration was assessed in ovariectomized rabbits. Li et al. [26] and Shirota et al. [28] studied ovariectomized rats. In two studies [24, 25], the PTH effect on osseointegration improvement was analyzed in orchiectomized rats. Dayer et al. conducted two studies [21, 22] to assess the PTH supplementation impact on implant osseointegration under protein undernutrition in rats. Kuchler et al. [15] evaluated the effect of PTH therapy on implant osseointegration in rats with streptozotocin (STZ)-induced diabetes. One study [23] assessed the impact of PTH supplementation using a rabbit model of cancellous bone loading. Valderrama et al. [16] evaluated the PTH bound to a synthetic matrix for guided bone regeneration around dental implants. Tsunori et al. [29] evaluated the effects of PTH on bone augmentation using a plastic cap in rat calvaria. The effectiveness of PTH coating to improve osseointegration in titanium implants was assessed by Yu et al. [30]. In 15 studies [12–15, 18–28], the PTH supplementation was administered subcutaneously and in one study [29] intraperitoneal, with a dosage ranged between 5 μg/kg/day and 100 μg/kg/day. In one study [16], the PTH was applied in a gel form, with a 1.6 μg/kg dose. Yu et al. [30] incorporated PTH (10 μg/mL and 100 μg/ml) in a biomimetic calcium phosphonate (CaP) implant coating via a co-precipitation method in a modified simulated body fluid (Table 1).

Implant-related characteristics of the studies included

In nine studies [12–16, 18–20, 27], 20–80 titanium implants were used. In seven studies [21, 22, 24–26, 28, 30], the number of titanium implants placed was not reported. Fahlgren et al. [23] used a stationary base with two bicortical screws, a movable loading core, and a top. In 16 studies [12–16, 18–22, 24–28, 30] dimensions (diameter × length in millimeters) of implants used ranged between 0.5 × 5 and 1 × 12 millimeters. In 14 studies [12–15, 18, 19, 21, 22, 24–28, 30] implants were placed in tibiae. In studies by Fahlgren et al. [23], Valderrama et al. [16], and Daugaard et al. [20], implants were placed in

Table 1 Characteristics of the studies included

Authors et al.	Study subjects (*n*)	Study groups	PTH Dose	Follow-up	Analysis Methods	Outcome
Daugaard et al. [12]	20 male dogs (average 13.8 months old)	Group 1: 10 control Group 2: 10 PTH	5 μg/kg/day SQ	4 weeks	HIST push-out	BIC was significantly higher in group-2 than group-1
Corsini et al. [13]	20 male rabbits (6 to 8 months old)	Group 1: 10 control Group 2: 10 PTH	6 μg/kg SQ 3 days/week	4 weeks and 8 weeks	Torque gauge manometer	Implant removal torque was significantly higher in group-2.
Mair et al. [14]	20 female rats (2 months old) 20 female rats (8 months old)	Group 1: 10 control. (8 months old) Group 2: 10 control (2 months old) Group 3: 10 PTH (8 months old) Group 4: 10 PTH (2 months old)	60 μg/kg SQ 3 days/week	4 weeks	HIST	Medullary BV/TV significantly improved in groups 3 and 4 compared to groups 1 and 2.
Kuchler et al. [15]	40 female rats (6 months old)	Group 1: 10 diabetes Group 2: 10 diabetes + PTH Group 3: 10 control Group 4: 10 control + PTH	60 μg/kg SQ 3 days/week	4 weeks	HIST	Bone formation and BIC significantly increased in groups 2 and 4.
Valderrama et al. [16]	6 dogs (24 months old)	Group 1: PEG Group 2: PEG + RGD Group 3: PEG + PTH Group 4: PEG + RGD + PTH	1.6 μg/kg gel	2 weeks and 4 weeks	HIST	Bone formation significantly improved in group-4. No BIC differences among the 4 groups.
Almagro et al. [18]	38 female rabbits (8 months old)	Group 1: 10 control Group 2: 14 OST + SAL Group 3: 14 OST+ PTH	10 μg/kg/day SQ 5 days/ week	12 weeks	Histology. SEM. Micro-CT	BIC and BMD was significantly higher in group-3 compared to groups 1 and 2.
Daugaard et al. [19]	20 male dogs (Age = NA)	Group 1: 10 control Group 2: PTH	5 μg/kg/day SQ	4 weeks	HIST push-out	BIC and BA were significantly higher in group 2 than group-1.
Dagaard et al. [20]	20 male dogs (average 13.8 months old)	Group 1: 10 Control Group 2: 10 PTH	5 μg/kg/day SQ	4 weeks	HIST push-out	Group-2 presented a significant increase in bone formation around implants.
Dayer et al. [21]	49 female rats (11 months old)	Group 1: 8 PTH + 15 % CAS Group 2:8 PTH + 2.5 % CAS Group 3: 9 PAM+ 15 % CAS Group 4: 8 PAM + 2.5 % CAS Group 5: 8 SAL + 2.5 CAS Group 6: SAL + 15 % CAS	4μug/kg SQ 5 days/week	8 weeks	Micro-CT Pull-out	BIC and BV/TV in group-1 and 2 were higher than other groups.
Dayer et al. [22]	41 female rats (10 months old)	Group 1: 8 15 % CAS Group 2:8 PTH + 2.5 % CAS Group 3: 9 PAM+ 2.5 % CAS Group 4: 8 Diet 2.5 % CAS Group 5: 8 Re-nutrition group[a]	40 μg/kg SQ 5 days/week	8 weeks	Micro-CT pull-out	BIC and BV/TV in groups 2 and 3 was significantly higher than the rest of the groups.
Fahlgren et al. [23]	104 male rabbits (minimum 7 months old)	Group 1: 13 SAL + LD + 0.5 MPa Group 2: 13 SAL + LD Group 3: 13 SAL+ LD + 1 MPa Group 4: 13 SAL Group 5: 13PTH + LD + 0.5 MPa Group 6: 13 PTH + LD Group 7: 13 PTH + LD + 1 MPa Group 8: 13 PTH	20 μg/kg/day 5 days/ week	4 weeks	Micro-CT compression testing. HIST inmunohistochemistry	BV/TV in groups 5 to 8 was significantly higher than groups 1-4

Table 1 (continued)

Authors et al.	Study subjects (*n*)	Study groups	PTH Dose	Follow-up	Analysis Methods	Outcome
Gabet et al. [24]	Male rats (13 weeks old) (*n* = NA)	Group 1: (*n* = NA) ORX + SAL Group 2: (*n* = NA) ORX + PTH Group 3: (*n* = NA) sham-ORX + SAL	25 μg/kg SQ 5 days/week	6 weeks	Micro-CT	BIC and BV/TV were significantly higher in group-2 compared to group 1 and 3.
Gabet et al. [25]	50 male rats (13 weeks old)	Group 1: 7 ORX + SAL Group 2: 6 ORX + PTH Group 3: 8 ORX + PTH Group 4: 8 ORX + PTH Group 5: 8 sham-ORX	Group 2: 5 μg/kg SQ 5 days/ week Group 3: 25 μg/kg SQ 5 days/ week Group 4: 75 μg/kg SQ 5 days/week	8 weeks	Micro-CT. Pull-out	BIC and BA were significantly higher in groups 2, 3 and 4, compared with group 1 and 5.
Li et al. [26]	50 female rats (3 months old)	Group 1: 10 OVX Group 2: 10 OVX + PTH Group 3: 10 OVX + ZA Group 4: 10 OVX + PTH + ZA	60 μg/kg SQ 3 days/week	12 weeks	Micro-CT histology push-out	BIC and BV/TV was significantly higher in groups 2 and 4, compared to groups 1 and 3.
Lima et al. [27]	48 female rats (Age = NA)	Group 1: 15 SAL Group 2: 16 CSI[b] + SAL. Group 3: 17 CSI[b] + PTH.	40 μg/kg SQ 3 days/ week	8.5 weeks	HIST	BIC and BA were significantly higher in group-3 compared with groups 1 and 2.
Shirota et al. [28]	72 female rats (12 weeks old)	Group 1: 24 Sham-operated Group 2: 24OVX only Group 3: 24 OVX + PTH	30 μg/kg SQ 3 days/week	1,2,4 and 8 weeks	HIST Histology	BMD was higher in groups 1 and 3 compared to group 2
Tsunori et al. [29]	30 Male rats (12 weeks old)	Group 1: SAL Group 2: PTH-35 μg/kg Group 3: PTH-105 μg/kg	Group 2: 35 μg/kg IP Group 3: 105 μg/kg IP 3 days/week	12 weeks	Micro-CT Histology HIST	BV increased significantly in group 2 and 3 compared to group 1.
Yu et al. [30]	12 Mice Gender = NA (12–15 week-old)	Group 1: 4 CaP coating (Control) Group 2: 4 CaP coat + PTH-10 μg/mL Group 3: 4 CaP coat + PTH-100 μg/mL	Group 2: 10 μg/mL Group 3: 100 μg/mL	4 weeks	Radiographs Micro-CT. HIST SEM	BIC and BA was significantly higher in group 3 compared to groups 1 and 2.

SAL saline solution, *OST* osteoporosis, *LD* loading device, *MPa* megapascal, *PAM* pamidronate, *CAS* casein diet, *PTH* parathyroid hormone, *Ti* titanium, *D* diameter, *L* length, *CSI* cigarette smoke inhalation, *BA* bone area, *BIC* bone-to-implant contact, *PMT* proportion of mineralized tissue, *HIST* histomorphometric analysis, *SEM* scanning electronic microscope, *BMD* bone mineral density, *CaP* calcium phosphates, *IP* intraperitoneal, *ORX* orchiectomy, *BV/TV* bone volume per tissue volume, *PEG* polyethylene glycol, *OVX* ovariectomized, *RGD* arginine-glycine-aspartic acid, *ZA* zoledronic acid, *SQ* subcutaneous, *Micro-CT* micro computed tomography

[a] CAS 2.5 % before implant placement, 15 % CAS after

[b] 60 days CSI prior and 60 days after surgery

the femur, mandible, and humerus, respectively. One study [29] examined calvaria defects to evaluate bone augmentation.

Cylindrical and screw-type implants were placed in five studies [12, 19, 20, 26, 30] and four studies [13, 15, 27, 28], respectively. In seven studies [14, 16, 18, 21, 22, 24, 25], the implant shape was not reported. Fahlgren et al. [23] used a loading device to assess if surgical trauma enhanced the anabolic effect of PTH on peri-implant bone volume fraction. Tsunori et al. [29] used a cylindrical plastic cap to evaluate the effect of PTH in a rat guided bone augmentation (GBA) model. In 11 studies [12, 16, 18–22, 24, 26, 27, 30], rough surfaced implants were used and in 2 studies [24, 25], the implants had smooth surfaces. The implant surface characteristics were not reported in five studies [13–15, 23, 28] (Table 2).

Assessment of osseointegration

In 11 studies [12, 14–16, 19, 20, 23, 27–30], osseointegration was assessed using histomorphometric analysis. In eight studies [12, 19–23, 25, 26], biomechanical testing was performed to assess new bone formation and strength of newly formed bone around implants. In nine studies [18, 21–26, 29, 30], new bone formation around implants was assessed using three-dimensional (3D) microcomputed tomography (micro-CT). In four studies [18, 26, 28, 29], osseointegration was assessed using histology. Almagro et al. [18] and Yu et al. [30] used scanning electron microscopy (SEM) to asses new bone formation around implants. Corsini et al. [13] assessed osseointegration using a torque gauge manometer. Immunohistochemistry was performed in the study by Fahlgren et al. [23].

Main outcomes

Results from 15 studies [12–15, 18–28] showed that subcutaneous PTH supplementation enhanced new bone formation and/or BIC around implants. In five studies [14, 15, 23, 25, 27], the PTH did not change the bone volume per tissue volume (BV/TV) or bone-to-implant contact (BIC) in the bone cortical compartment (cancellous bone). Results by Valderrama et al. [16] showed that the effect of binding PTH to RGD-modified hydrogel marginally significantly improved bone formation at 2 weeks of healing. One study [13] reported

Table 2 Characteristics of the implants included

Authors et al.	Number of implants (*n*)	Implant dimensions (D × L in mm)	Location of implant placement	Implant Shape	Implant Surface Characteristics
Daugaard et al. [12]	20 Ti implants	6.13 × 10	Tibia	Cylindrical	Porous coated
Corsini et al. [13]	20 Ti implants	3.75 × 8	Tibia	Screw	NA
Mair et al. [14]	80 Ti implants	1 × 3	Tibia	NA	NA
Kuchler et al. [15]	40 Ti implants	1 × 3	Tibia	Screw	NA
Valderrama et al. [16]	48 Ti implants	2.8 × 8	Mandible	NA	Large-grit (Sanblast + etch)
Almagro et al. [18]	38 Ti implants	2.5 × 7	Tibia	NA	Rough
Daugaard et al. [19]	20 Ti implants	6 × 10	Tibia	Cylindrical	Porous coated
Dagaard et al. [20]	20 Ti implants	5.95 × 10.94	Humerus	Cylindrical	Porous coated
Dayer et al. [21]	Titanium NA	1 × 4.1	Tibia	NA	Rough (Sandblast + etch)
Dayer et al. [22]	Titanium NA	1 × 4.1	Tibia	NA	Rough (Sandblast + etch)
Fahlgren et al. [23]	NA	NA	Femur	Stationary base with 2 bicortical screws, a movable loading core and a top.	NA
Gabet et al. [24] Type 2: Rough (Sandblast + etch)	Titanium NA	NA	Tibia	NA	Type 1: Smooth
Gabet et al. [25]	Titanium NA	0.9 × 5	Tibia	NA	Smooth
Li et al. [26]	Titanium NA	1 × 12 mm	Tibia	Cylindrical	Rough (Grit-blasted + Hydroxyapatite coat)
Lima et al. [27]	48 Ti implants	2.2 × 4	Tibia	Screw	Rough (Blasted)
Shirota et al. [28]	Titanium implants NA	2 × 5	Tibia	Screw	NA
Tsunori et al. [29]	Plastic cap	NA	Calvaria	NA	NA
Yu et al. [30]	Titanium cylinders NA	0.5 × 5	Tibia	NA	Rough

NA Not available, *Ti* titanium

that PTH enhanced the removal torque on implants. Yu et al. [30] suggested that PTH can be incorporated into CaP coatings to improve osseointegration of titanium implants.

Li et al. [26] reported that PTH combined with zoledronic acid (ZA) treatment showed stronger effects than each treatment alone in induced-osteoporosis in rats. According to Dayer et al. [21, 22], PTH reversed the deleterious effects of long-term protein undernutrition on mechanical fixation, and improves osseointegration more than pamidronate or renutrition in rats. One study [23] concluded that PTH enhanced peri-implant bone volume fraction by 30 % in loaded bone (Table 1).

Quality assessment of included studies

Quality assessment [17] showed that all studies were conducted on experimental animals and the total quality score ranged from 8 to 10. The most common shortcoming among all studies was the short term and incomplete follow up of the experimental groups. Furthermore, as all studies were performed in animals, the application of these results to human population is still limited. Thus, on average, the quality of included animal studies on the impact of PTH on the osseointegration of implants was good, limitations of short-term follow up and lack of clinical studies limit the clinical application of these study outcomes. Quality assessment of the individual papers is summarized in Table 3.

Discussion

Results from 94 % of the studies [12–15, 18–30] included in the present systematic review reported that intermittent PTH therapy is effective enhancing new bone formation around implants. It is speculated that intermittent PTH administration enhances osseointegration. However, it seems difficult to replicate these experimental results in a clinical setting due to a number of reasons. Firstly, it seems exigent to estimate a precise dosage of PTH delivery that could yield the most predictive outcome (in terms of new bone formation). For example, in the studies of Daugaard et al. [12, 19, 20] PTH was administered to study subjects at a dosage of 5 μg/kg/day; whereas in studies by Lima et al. [27] and Gabet et al. [24, 25], PTH therapy was delivered at dosages of 40 μg/kg/3 days a week and up to 75 μg/kg/5 days weekly, respectively. Moreover, the frequency of PTH therapy also varied between the studies [12–16, 18–30] assessed. For example, in the studies by Daugaard et al. [12, 19, 20], PTH was administered subcutaneously daily for 4 weeks; whereas Lima et al. [27] subcutaneously administered PTH to study subjects three times a week for up to 8.5 weeks. This reflects that there is a lack of consensus regarding the dosage and frequency of PTH delivery in the studies included. Furthermore, these experimental studies [12–16, 18–30] were performed for a maximum follow-up period of 12-weeks. It seems challenging to implement these dosages and frequencies of PTH therapy in a clinical setting.

Table 3 CASP quality assessment of the reviewed papers

Authors	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total quality score (0 to 12)
Daugaard et al. [12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	10
Corsini et al. [13]	Yes	Yes	Yes	Yes (implant removal torque)	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Mair et al. [14]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Kuchler et al. [15]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	9
Valderrama et al. [16]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	8
Almagro et al. [18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Daugaard et al. [19]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Daugaard et al. [20]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Dayer et al. [21]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Dayer et al. [22]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Fahlgren et al. [23]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	9
Gabet et al. [24]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Gabet et al. [25]	Yes	Yes	Yes	No (only anchorage was assessed)	Yes	No	Yes	Yes	Yes	Yes	Yes	No	10
Li et al. [26]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Lima et al. [27]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Shirota et al. [28]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Tsunori et al. [29]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10
Yu et al. [30]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10

Studies [31, 32] have shown that habitual smoking jeopardizes osseointegration by enhancing bone resorption around implants. Lima et al. [27] assessed the effect of tobacco smoke exposure and the efficacy of PTH therapy in promoting osseointegration; in this study [27], rats were exposed to cigarette smoke for approximately 8 weeks after PTH therapy. The results showed significantly more bone formation in PTH-treated group compared to controls, regardless of the exposure to cigarette smoke. The authors of the present systematic review perceive that experimental results by Lima et al. [27] are unable to replicate a clinical scenario of cigarette smoking and one of the major factors for this perception was the short follow-up period (8 weeks). We hypothesize that chronic tobacco smokers (for example individuals smoking >20 cigarettes daily for at least 20 years) exhibit significantly more bone resorption around implants compared to smokers with a relatively shorter history of smoking habit. Nevertheless, further clinical randomized controlled trials are needed to test this hypothesis.

It is well known that implant surface characteristics play an essential role in osseointegration promotion around implants [33–35]. Several studies have shown that osteoblastic proliferation is higher around rough-surfaced implants compared to implants with machined/smooth surfaces. From the literature reviewed, it is noteworthy that nearly 56 % studies used rough surfaced implants. It is tempting to speculate that in addition to PTH delivery, also the implant surface roughness may have contributed in enhancing new bone formation by attracting osteoprogenitor cells toward implants surfaces. Results by Gabet et al. [24, 25] showed significantly more new bone formation around implants (regardless of their surface characteristics) in animals injected with PTH, compared to untreated experimental animals. However, these are short-term follow-up (up to 8 weeks) results. Moreover, results by Gabet et al. [24, 25] were based on micro-CT and biomechanical testing. Although micro-CT is a valuable three-dimensional imaging technology, histological analysis is the *gold standard* for assessing new bone formation around implants[36].

It is pertinent to mention that in all the studies [12–16, 18–30] included in the present systematic review, the implants were placed in dense compact bones (tibiae, humerus, calvaria, and mandible). It has been reported that one of the factors that influences the success rate of implants is bone density [37]. According to Jaffin and Berman [37], the success rate of implants is significantly higher in dense compact bones compared with bones with thin cortex and poor medullary strength. Therefore, from a clinical perspective, it is hypothesized that the efficacy of PTH therapy on implant osseointegration, varies between the maxilla and the mandible. However, further prospective clinical trials are needed to test this hypothesis. Moreover, in the studies included [12–16, 18–30], different outcome variables, such as BIC, BV/TV and torque removal were used to evaluate osseointegration. These parameters could not be directly compared in different experimental models. Furthermore, it is notable that none of the articles reported any adverse effects associated with systemic PTH administration. A study in rats by Vahle et al. [38] reported that daily administration of PTH at a dosage of 75 μg/kg/day for 24 months resulted in a mean incidence (21 to 31 %) of osteosarcoma. Another study conducted in rats by Sato et al. [39] reported increased brittleness and reduction of marrow spaces of the femoral midshaft after 1 year of treatment with 0, 8, or 40 μg/kg/day subcutaneous PTH supplementation. These findings should be taken in consideration in a future protocol for the clinical use of PTH in implantology, including low doses and short-term administration periods.

Within the limits of the present systematic review, the effects of PTH delivery in osseointegration remain debatable, and further randomized control trials are needed.

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Appendix. List of excluded studies. Reason for exclusion is shown in parenthesis

a. Micksch T, Herrmann E, Scharnweber D, Schwenzer B. (2015) A modular peptide-based immobilization system for ZrO2, TiZr and TiO2 surfaces. Acta Biomater 12:290–297. (Focused question was not answered)

b. Ross RD, Hamilton JL, Wilson BM, Sumner DR, Virdi AS. (2014) Pharmacologic augmentation of implant fixation in osteopenic bone. Curr Osteoporos Rep 12:55–64. (Review article)

c. Prati AJ, Casati MZ, Ribeiro FV, Cirano FR, Pastore GP, et al. (2013) Release of bone markers in immediately loaded and nonloaded dental implants: a randomized clinical trial. J Dent Res. 2013;92(12 Suppl):161S-7S. (Focused question was not answered)

d. Zou H, Zhao X, Sun N, Zhang S, Sato T, et al. (2013) Effect of chronic kidney disease on the healing of titanium implants. Bone 56:410–415. (Focused question was not answered)

e. Tanaka S, Hata K, Yoneda T. (2012) Potential use of parathyroid hormone (PTH) in the treatments for oral diseases. Clin Calcium 22:75–82. (Review article.)

f. Zeng X, He H, Zhang L, Wu Y, Wang Y, et al. (2011) A potential therapeutic approach to overload-induced bone loss around implant: parathyroid hormone (PTH). Med Hypotheses 77:701–704. (Focused question was not answered)

g. Oteo-Álvaro Á, Matas JA, Alonso-Farto JC. (2011) Teriparatide (rh [1–34] PTH) improved osteointegration of a hemiarthroplasty with signs of aseptic loosening. Orthopedics 34:e574-e577. (Focused question was not answered)

h. Aggarwal P, Zavras A. (2012) Parathyroid hormone and its effects on dental tissues. Oral Dis 18:48–54 (Focused question was not answered)

i. Kuchler U, Luvizuto ER, Tangl S, Watzek G, Gruber R. (2011) Short-term teriparatide delivery and osseointegration: a clinical feasibility study. J Dent Res 90:1001–1006. (Focused question was not answered)

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