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SYSTEMATIC REVIEW

Does incorporating zinc in titanium implant surfaces influence osseointegration? A systematic review

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ABSTRACT

Statement of problem. Titanium implant surfaces have been modified to improve osseointegration; however, the evidence for incorporating zinc into titanium implants to improve new bone formation and osseointegration is not clear.

Purpose. The purpose of this systematic review was to assess the efficacy of treating titanium surfaces with zinc on the osseointegration of implants.

Material and methods. The focused question addressed was, "Does incorporating zinc in titanium implant surfaces influence osseointegration?" Indexed databases were searched up to January 2016 using the key words "Bone to implant contact"; "implant"; "zinc"; "osseointegration." Letters to the editor, case reports/case series, historic reviews, and commentaries were excluded. The pattern of the review was customized to summarize the pertinent data.

Results. Ten experimental studies were included, all of which were performed in animals (5 in rabbits, 4 in rodents, and 1 in goats). The number of titanium implants placed ranged from 10 to 78. The results from all studies showed that incorporating zinc into titanium implants enhanced new bone formation and/or bone-to-implant contact around implants. One study reported that zinc enhanced the removal torque on implants.

Conclusions. The current available evidence on adding zinc to titanium implants surfaces to enhance osseointegration remains unclear. Further investigation is necessary to assess its effectiveness and safety in humans and to establish a standard methodology and ideal compound for incorporating zinc ion into titanium implant surfaces in a clinical setting. (J Prosthet Dent 2016;■:■-■)

Osseointegration is a key factor in the long-term success and survival of implants. The overall success and predictability of dental implant treatment depends on the primary stability, formation of direct bone-to-implant contact (BIC), and quantity and/or quality of residual bone. In addition, implant materials must demonstrate favorable mechanical properties and biocompatibility.[1-3] Titanium (Ti) is considered the ideal material for dental implants,[4] and several strategies such as surface coatings,[2,5] ion incorporation,[6,7] and chemical grafting[8] have been studied to enhance bone formation around Ti implants. Furthermore, adjunctive treatments such as vitamin D supplementation and hormone replacement have been reported to enhance BIC and new bone formation (NBF), thereby improving the success and survival rate of dental implants.[2,5]

Zinc (Zn) is an essential trace element that plays an important role in biologic osseous functions such as mineralization, hormone activity, and DNA synthesis.[9] Zn deficiency results in delayed skeletal growth and

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Clinical Implications

Incorporating zinc in titanium implants to promote new bone formation has shown promising results in animal models; however, further investigation is necessary to assess its effectiveness in humans.

bone development, postmenopausal osteoporosis, and osteopenia.[10,11] Zn induces bone formation by aminoacyl-tRNA synthetase and runt-related transcription factor 2 (RUNX2) activation, stimulating cellular protein synthesis (such as collagen and alkaline phosphatase) and osteoblastic activity.[12-14] Furthermore, Zn inhibits osteoclastic bone resorption, stimulates cellular apoptosis of mature osteoclasts, and has demonstrated important antibacterial properties.[12,15,16] The incorporation of Zn ion into bioceramics, bioglasses, bone cements, and Ti implant coatings has therefore been proposed to enhance their mechanical properties and promote osteogenic cell adhesion, proliferation, and differentiation.[15,17-19] In an experimental study on 3-month-old ovariectomized (OVX) rats, Li et al[20] investigated the effect on implant osseointegration of incorporating Zn in the hydroxyapatite (HA) coating on Ti surfaces. The results were based on fluorescence labeling, 3-dimensional microcomputed tomography (micro-CT), and histologic, biomechanical, and histomorphometric analysis. The results showed a higher mineral apposition rate for periimplant bone, bone area ratio, and BIC in Zn-treated implants than in controls. Moreover, in contrast with the control group, Zn also considerably increased the strength of the bone. Likewise, Shen et al[21] reported higher NBF, BIC, and shear strength around Ti implants modified with Zn placed in rabbits compared with the control group. Similar results have been reported in other preclinical studies.[22,23]

The purpose of the present study was to systematically review the efficacy of treating Ti surfaces with Zn on the osseointegration of implants.

MATERIAL AND METHODS

Based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a specific question was constructed according to the Participants, Interventions, Control, Outcomes (PICO) principle (Fig. 1). The addressed focused question was, "Does incorporating zinc in titanium implant surfaces influence osseointegration?"

(P) Participants: Participants must have undergone implant treatment.
(I) Types of interventions: The intervention of interest was the effect of zinc on osseointegration.
(C) Control intervention: Osseointegration without zinc incorporation.
(O) Outcome measures: BIC, NBF, and/or percent bone volume around implants with and without zinc.

The eligibility criteria were as follows: original studies, clinical studies, experimental studies, inclusion of a control group (osseointegration around implants without Zn), and intervention: effect of Zn ion on osseointegration. Letters to the editor, historic reviews, commentaries, case series, and case reports were excluded.

PubMed/Medline (National Library of Medicine), EMBASE, Scopus, Web of knowledge, and Google-Scholar databases were searched up to January 2016 using various combination of the following keywords: zinc + bone to implant contact; zinc + coating + implants; zinc + implants + osseointegration; zinc + osseointegration; zinc + supplementation + implants; zinc + osseointegration + supplementation; zinc + supplementation + bone to implant contact; dental + implants + zinc + osseointegration; implants + zinc. Titles and abstracts of studies identified using the above-described protocol were screened by 2 authors (S.V.K. and F.J.) and checked for agreement. The full texts of studies judged to be relevant by title and abstract were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand searched to identify any studies unidentified in the previous step. Once again, the articles were checked for disagreement by discussion among the authors (Fig. 1). Kappa scores (Cohen kappa coefficient) were used to determine the level of agreement between the 2 reviewers.[24]

A quality assessment of included studies was performed to increase the strength of the systematic review. Ten studies[20-23,25-30] were included and underwent a quality assessment with the Critical Appraisal Skills Program (CASP) Cohort Study Checklist.[31] The CASP tool uses a systematic approach based on the following 12 specific criteria: study issue is clearly focused; cohort is recruited in an acceptable way; exposure (Zn incorporation) is accurately measured; outcome (osseointegration and/or NBF around Ti implants) is accurately measured; confounding factors are addressed; follow-up is long and complete; results are clear; results are precise; results are credible; results can be applied to the local population; results fit with available evidence; there are important clinical implications. Each criterion received a response of "Yes," "No," or ''cannot tell." Each study had a possible maximum score of 12. CASP scores were used to grade the methodologic quality of each study assessed in the present systematic review.

RESULTS

Study selection and characteristics

The initial search identified 414 articles. After abstract screening, 396 did not answer the focused question or were

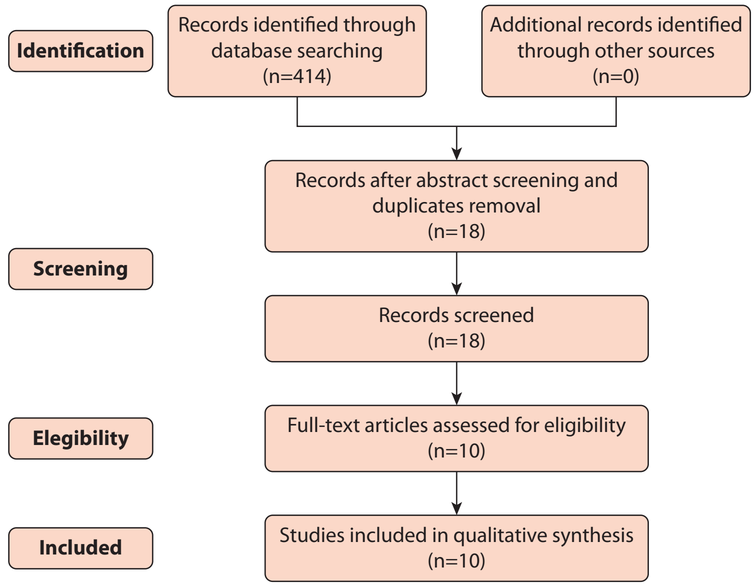

Figure 1. Article selection flow chart for systematic reviews according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

duplicates. In the second step of evaluation, 8 more articles that did not answer the focused question were excluded. In total, 10 prospective and in vivo studies[20-23,25-30] were included. Five studies[21-23,28,30] were performed in rabbits; 4 studies[20,25,27,29] were performed in rodents, and in 1 study, male and female goats were used as study subjects.[26] Two studies[22,23] were performed in male rabbits, and 3 studies[21,28,30] performed in rabbits did not specify sex. In 3 studies,[20,25,29] female rats were used as study subjects, and 1 study[27] was performed in male rats. In all studies,[20-23,25-30] the follow-up period ranged between 3 days and 26 weeks.

In the studies by Li et al[20] and Zhang et al,[29] the effectiveness of incorporating Zn into Ti implants was assessed in OVX rats. Alvarez et al[22] incorporated Zn into Ti implants surfaces using a hydrothermal process (HTP) with zincate ($[Zn(OH)_4]^{2-}$) solution; Li et al[25] used Zn acetate solutions. Mistry et al[26] used plasma-spray technology to coat Ti implants with Zn-doped hydroxyapatite (HA), and Yu et al[28] used hardystonite, a Zn-incorporated calcium silicate-based ceramic ($Ca_2ZnSi_2O_7$). In 1 study,[28] 3 different types of Zn/Ag microgalvanic couples were fabricated on Ti by plasma immersion ion implantation (PIII) to investigate the Zn antibacterial and osseointegration properties. Qiao et al[27] investigated the osteogenic capability of incorporating different amounts of Zn into the surface of Ti implants by means of 2 different techniques, PIII and plasma electrolytic oxidation (PEO) with Zn acetate dihydrate. Li et al[20] studied Zn-incorporated coating on Ti implants using the sol-gel method technique with zinc nitrate hexahydrate ($Zn(NO_3)_2.6H_2O$) dip coating, and Shen et al[21] used zinc chloride ($ZnCl_2$) solution spin-coating. In 2 studies,[29,30] electromechanical deposition using zinc nitrate ($Zn(NO_3)_2$) or $ZnCl_2$ was used to modify Ti implant surfaces to study the potential of Zn for BIC and NBF improvement (Table 1).

Implant-related characteristics of the studies included

In 6 studies,[22,26-30] between 10 and 78 Ti implants were used. In 4 studies,[20,21,23,25] the number of Ti implants used was not reported. In 9 studies,[20-22,25-30] the dimensions (diameter×length mm) of the implants used ranged between 0.8×10 mm and 1.1×120 mm. One study[23] did not report the dimensions of the implants. In 5 studies,[20-22,27,28] the implants were placed in the femur. In 3 studies,[23,25,29] the implants were placed in the tibia. In 1 study,[26] they were placed in the humerus. Zhao et al[30] placed implants in the femur and the tibia. Cylindrical implants were placed in 8 studies,[20-23,25-28] and screw-type implants were placed in 2 studies.[29,30] In 4 studies,[20,25,29,30] rough-surfaced implants were used, and in 6 studies,[21-23,26-28] smooth and rough-surfaced implants were used (Table 2).

Assessment of osseointegration

In 6 studies,[20,21,23,26-28] osseointegration was assessed by using histologic analysis. Jin et al[23] used histologic evaluation to assess Zn antimicrobial ability. In 6 studies,[20-22,25,26,30] biomechanical testing (push-out or removal torque) was performed to assess NBF and the strength of newly formed bone around implants. In 5 studies,[20,21,23,25,26] NBF around implants was assessed using micro-CT. In 4 studies,[20,28-30] osseointegration was assessed using histomorphometric analysis. Alvarez et al,[22] Mistry et al,[26] and Qiao et al[27] used scanning

Table 1. Characteristics of included studies

Author	Study Subjects, n (Age)	Study Groups	Zinc Incorporation Method	Follow-up	Analysis Methods	Outcome
Alvarez et al[22]	9 Male rabbits (NA)	Group 1: Ti smooth surface (control) Group 2: Ti rough surface Group 3: Zn + Ti smooth surface Group 4: Zn + Ti rough surface	HTP with $[Zn(OH)_4]^{2-}$ 300 mL solution Zn detection limit: 0.012 ppm	4, 8, and 12 wk	Push-out test SEM/EDX	Group 3 and 4 presented significantly higher BIC and shear strength compared with groups 1 and 2. After week 4 no significant difference between groups 3 and 4.
Jin et al[23]	Male rabbits (NA)	Group 1: Ti smooth surface (Control) Group 2: Zn dual Ag PIII Group 3: Zn prior Ag PIII Group 4: Ag prior Zn PIII	Zn PIII Voltage: −30 kV PF: 5 Hz Time: 90 min	3 d, 2, 4, and 6 wk	Radiograph Micro-CT Histology	Group 2 presented significantly higher BIC, NBF and better antibacterial properties compared with groups 1, 3 and 4.
Li et al[20]	32 Female rats (3 mo)	Group 1: 14 OVX + HA Group 2: 14 OVX + HA + Zn	Sol-gel dip coating $Zn(NO_3)_2.6H_2O$ Coating: 1 μm	6 and 12 wk	Double FL Histology HIST Micro-CT Push-out test	Group 2 presented higher MAR, BV/TV, BA, BIC and shear strength compared with group 1.
Li et al[25]	32 Female rats (1 mo)	Group 1: 8 Ti (Control) Group 2: 8 Ti-NT_S Group 3: 8 Ti-NT_S + Zn (1h HTP) Group 4: 8 Ti-NT_S + Zn (3h HTP)	HTP Zn acetate 0.1 M 40 mL solution Group 3: 3.5 μg Group 4: 60.1 μg	4 wk	Micro-CT Push-out test	Group 3 and 4 presented significantly higher NBF, and shear strength compared with groups 1 and 2.
Mistry et al[26]	6 Female goats 6 Male goats (12 to15 mo)	Group 1: Ti smooth surface (Control) Group 2: HA Group 3: Zn + HA Group 4: HTP	Plasma sprayed Group 3 coating: 100-150 μm (5% ZnHA)	6, 12, and 26 wk	Radiograph Micro-CT SEM/EDX Histology Push-out test	Group 3 and 4 presented significantly higher BIC and NBF compared to groups 1 and 2. Group 4 presented higher shear strength compared to groups 1, 2 and 3.
Qiao et al[27]	5 Male rats (12 wk)	Group 1: Ti smooth surface (Control) Group 2: ZnO (Control) Group 3: PEO-Z1 Group 4: PEO-Z2 Group 5: Z0-PIII-Zn	PEO: Group 3: 0.02 M Group 4: 0.06 M Zn acetate dihydrate PIII: Group 5: Zn Voltage: 15 kV PF: 6 Hz Time: 120 min	12 wk	Sequential FL Histology SEM/EDX	Group 5 presented higher NBF and BIC compared with groups 1,2,3 and 4.
Shen et al[21]	60 Rabbits (NA)	Group 1: Ti smooth surface (Control) Group 2: Ti rough surface (HF etch) Group 3:Ti + Zn	$ZnCl_2$ solution Sol-gel spin- coating and calcination Group 3: 0.16 M	4 and 12 wk	Radiograph Micro-CT Push-out test Histology	Group 3 presented higher NBF, BIC and shear strength compared with groups 1 and 2.
Yu et al[28]	9 Rabbits (NA)	Group 1: Ti smooth surface (Control) Group 2: Ti + $CaSiO_3$ Group 3: Ti + $Ca_2ZnSi_2O_7$	Plasma sprayed $Ca_2ZnSi_2O_7$ Group 3 coating: 170 μm	6 wk	Histology HIST	Group 3 presented higher NBF and BIC compared with groups 1 and 2.
Zhang et al[29]	36 Female rats (3 mo)	Group 1: 9 OVX + HA (Control) Group 2: 9 OVX + HA + Zn Group 3: 9 OVX + HA + Mg Group 4: 9 OVX + HA + Sr	Electromechanical deposition Group 2: $ZnCl_2$ 2.5% M	4, 8, and 12 wk	HIST	Groups 2 and 4 presented higher NBF and BIC compared with groups 1 and 3.
Zhao et al[30]	Rabbits (NA)	Group1: HA (Control) Group 2: HA + Zn	$Zn(NO_3)_2$ Electromechanical deposition	2, 4, and 8 wk	HIST Removal torque	Group 2 presented higher NBF, BIC and shear strength compared with group 1.

Zn, zinc; Ti, titanium; SEM, scanning electron microscopy; EDX, energy dispersive x-ray analyzer; Ag, silver; h, hour; BIC, bone-to-implant contact; PIII, plasma immersion ion implantation; micro-CT, microcomputed tomography; Sr, strontium; HA, hydroxyapatite; OVX, ovariectomized; NBF, new bone formation; FL, fluorescence labeling; Mg, magnesium; HIST, histomorphometry; MAR, mineral apposition rate; BA, bone area ratio; BV/TV, percent bone volume; PF, pulsing frequency; Ti-NT_S, titania nanotubes; HTP, hydrothermal process; PEO, plasma electrolytic oxidation; ZnO, zinc-free; HF, hydrofluoric acid.

electron microscopy/energy-dispersive x-ray spectroscopy (SEM/EDX) to assess NBF around implants. In 2 studies,[20,27] fluorescence labeling was used to assess NBF and the mineralization process around the implants. In 3 studies,[21,23,26] radiographs were used to assess NBF.

Table 2. Characteristics of included implants

Author	Implants (n)	Implant Dimensions, D×L (mm)	Location of Implant Placement	Implant Shape	Implant Surface Characteristics
Alvarez et al[22]	Ti implants (20)	2×5	Femur	Cylindrical	Smooth Rough (MGT)
Jin et al[23]	Ti implants (NA)	NA	Tibia	Cylindrical	Smooth Rough
Li et al[20]	Ti implants (NA)	1.1×120	Femur	Cylindrical	Rough (APA+AE)
Li et al[25]	Ti implants (NA)	0.8×10	Tibia	Cylindrical	Rough
Mistry et al[26]	Ti implants (48)	3×6	Humerus	Cylindrical	Smooth Rough
Qiao et al[27]	Ti implants (10)	2×7	Femur	Cylindrical	Smooth Rough
Shen et al[21]	Ti implants (NA)	3×13	Femur	Cylindrical	Smooth Rough (AE)
Yu et al[28]	Ti implants (54)	1×10	Femur	Cylindrical	Smooth Rough (SB)
Zhang et al[29]	Ti implants (72)	2×6	Tibia	Screw	Rough (APA+AE)
Zhao et al[30]	Ti implants (78)	3×10	Femur and tibia	Screw	Rough (APA+AE)

MGT, mechanical ground treatment; APA, airborne-particle abraded; AE, acid-etched.

Table 3. CASP quality assessment of reviewed papers

Author	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)
Alvarez et al[22]	X	X	X				X	X	X		X	X	8
Jin et al[23]	X	X	X	X			X	X	X		X	X	9
Li et al[20]	X	X	X	X			X	X	X		X	X	9
Li et al[25]	X	X	X				X	X	X		X	X	8
Mistry et al[26]	X	X	X	X		X	X	X	X		X	X	10
Qiao et al[27]	X	X	X	X			X	X	X		X	X	9
Shen et al[21]	X	X	X	X			X	X	X		X	X	9
Yu et al[28]	X	X	X	X			X	X	X		X	X	9
Zhang et al[29]	X	X	X	X			X	X	X		X	X	9
Zhao et al[30]	X	X	X	X			X	X	X		X	X	9

Main outcomes

The results from all studies[20-23,25-30] showed that incorporating Zn into Ti implants enhanced NBF and/or BIC around implants. Li et al[20] and Zhang et al[29] reported that Zn bound to HA presented higher NBF and BIC than HA coating alone in rats with induced-osteoporosis. One study[29] reported that strontium combined with HA coating presented higher BIC than Zn combined with HA coating. One study[30] reported that Zn enhanced the removal torque on implants. Yu et al[28] suggested that a Zn ceramic coating improved the osseointegration of Ti implants. According to Qiao et al,[27] Zn coatings by PIII presented higher NBF and BIC compared with Zn coatings by PEO.

Quality assessment of included studies

The quality assessment showed that the total quality score ranged between 8 and 10. The most common shortcoming among all studies was the lack of confounding factor assessment and short-term and incomplete follow-up of the experimental groups. Furthermore, because all studies were performed in animals, these results cannot apply to the human population. Overall, the quality of the included studies was good, although limitations of short-term follow-up and lack of clinical studies limit the clinical application of their outcomes. The quality assessment of the individual papers is summarized in Table 3.

DISCUSSION

To our knowledge, the present study is the first to systematically review the efficacy of incorporating Zn into Ti implants to enhance osseointegration and NBF. Because the studies included in the present systematic review[20-23,25-30] all reported that incorporating Zn into Ti implants enhanced NBF, it is tempting to speculate that Zn enhances osseointegration. However, a number of factors make it difficult to replicate these experimental results in a clinical setting. First, a reliable and accurate method of incorporating Zn ion into Ti implant surfaces to predictably improve NBF must be established. For example, Zhang et al[29] and Zhao et al[32] used electromechanical deposition to modify Ti implants surfaces, whereas, Alvarez et al[22] and Li et al[25] incorporated Zn into Ti implants surfaces using HTP. Moreover, the Zn chemical compound also varied among the studies assessed. For example, Alvarez et al[22] used a 300-mL ($[Zn(OH)_4]^2$) solution to incorporate the Zn into Ti surfaces, whereas Li et al[25] used a 40-mL Zn acetate solution. This reflects a lack of consensus regarding the Zn chemical compound and the surface modification method in the studies included. The challenge must be to implement a specific method and select a specific Zn compound for incorporating this ion into Ti implants surfaces in a clinical setting.

Furthermore, because the experimental studies[20-23,25-30] were performed for a maximum follow-up period of 26 weeks, it remains unclear whether the BIC of patients receiving Zn incorporated Ti dental implants would increase and contribute to their long-term success and survival. Long-term clinical studies are needed in this regard. The authors, however, emphasize that increasing the follow-up time of the studies[20-23,25-30] included in the present systematic review would have provided stronger evidence regarding the efficacy of incorporating Zn into Ti implants on osseointegration.

All studies[20-23,25-30] used rough-surfaced implants. Alvarez et al[22] showed greater NBF around Zn-treated implants (regardless of their surface characteristics) compared with untreated implants. However, the result is from a short-term follow-up (up to 12 weeks). Because implant surface roughness plays an essential role in enhancing osseointegration by attracting osteoprogenitor cells toward implants surfaces,[5] the addition of Zn may further enhance surface roughness of implants, thereby increasing NBF. This hypothesis is a possible source of bias in these studies.[20-23,25-30] Further well-designed studies are needed to justify the contribution of Zn itself in promoting osseointegration.

Among the studies[20-23,25-30] that fulfilled our eligibility criteria, the methods used to assess osseointegration varied. For example, Jin et al[23] and Mistry et al[26] used micro-CT, radiographs, and histology to assess BIC and NBF around implants, whereas Zhang et al[29] used only histomorphometric analysis to assess osseointegration. In another study,[22] SEM/EDX and push-out tests were used to assess BIC, leaving the precise method of assessing BIC unclear. Although a variety of methods can be used to assess BIC and NBF (biomechanical testing, micro-CT), histologic evaluation continues to be the gold standard.

Confounding parameters such as poorly controlled diabetes mellitus, increasing age, stress, deficient oral hygiene, and tobacco use may also influence healing and are significant risk factors for alveolar bone loss.[33-40] Because all studies[20-23,25-30] included in this systematic review were performed in animals, additional studies are required to determine whether Ti implant surfaces modified with Zn in a clinical scenario would facilitate NBF in patients with poor plaque control, the elderly, the systemically compromised, or tobacco product users.

Zn systemic overdose may cause hyperglycemia, neurotoxicity, and other adverse reactions.[41,42] Furthermore, Yamamoto et al[43] showed that Zn concentrations greater than 5.88 mg/L may have cytotoxic effects on cells, and Roguska et al[44] reported that increasing the Zn oxide content in Ag nanoparticles co-deposited onto the surfaces of Ti implants increased the adhesion of bacterial cells. Excess Zn in Ti implants could be distributed and absorbed in the organism through the bloodstream and induce local and/or systemic adverse effects. Any future protocol for the clinical incorporation of Zn in implantology should include low doses and Zn slow release.

CONCLUSIONS

The current available evidence is unclear as to the influence of adding zinc to titanium implant surfaces in an attempt to enhance osseointegration. Effectiveness and safety in humans, a standard methodology, and the ideal compound for incorporating zinc ion into titanium implant surfaces should be investigated in a clinical setting.

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