Role of Osteogenic Coatings on Implant Surfaces in Promoting Bone-To-Implant Contact in Experimental Osteoporosis: A Systematic Review and Meta-Analysis

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Objective: *The aim of this systematic review and meta-analysis was to evaluate the role of osteogenic coatings (placement of a thin film of organic and inorganic osteoinductive and osteoproliferative materials) on implant surfaces in augmenting bone-to-implant contact (BIC) in osteoporotic bone.*

Data Sources: *To answer the focused question "Do osteogenic coatings on implant surfaces increase BIC in osteoporotic bone?" PubMed/MEDLINE, EMBASE, ISI Web of Knowledge, Scopus, and Google-Scholar databases were searched till June 2017 using different combinations of the following key words: bone-to-implant contact, coating, implant surface, osseointegration, and osteoporosis. Letters to the Editor, review articles, case-reports/case-series, and commentaries were excluded.*

Results: *Six animal studies were included, in which osteoporosis was induced by bilateral ovariectomy. In all studies, implant surface roughness was increased by various osteogenic surface coatings including alumina, hydroxyapatite, calcium phosphate, and zoledronic acid. Five studies showed that bone volume and BIC are significantly higher around implants with coated surfaces than noncoated implants. In 1 study, there was no difference in BIC around coated and noncoated implants.*

Conclusion: *Although experimental studies have shown that osteogenic coatings are effective in enhancing BIC, their clinical relevance requires further investigations. (Implant Dent 2017;00:1–8)*

Key Words: osseointegration, new bone formation, osteogenesis, surface modification

Formation of a direct bone-to-implant contact (BIC) is an important parameter, which influences the overall success and survival of dental implant therapy.[1–4] One of the factors that have been reported to affect BIC is surface characteristics of the implant. It has been reported that osteoblastic attachment and collagen synthesis are significantly higher around rough-surfaced implants in contrast to implants with machined surfaces.[5,6] Therefore, some investigators have used implants with organic and inorganic osteogenic coatings in an attempt to improve implant surface activity and osteopromotive activity.[7–12]

Osteoporosis is a metabolic disease of bone, which is characterized by low bone mineral density and reduced bone mass because of an imbalance in the activity of osteoblasts and osteoclasts.[13,14] Premenopausal and postmenopausal estrogen deficiency, excessive glucocorticoid intake, eating disorders (such as anorexia nervosa and celiac disease) have been related with the etiology of osteoporosis.[15–17] Although bone quality and strength are compromised in osteoporotic patients; osteoporosis is not considered a contraindication for implant placement.[18,19]

It is hypothesized that osteogenic coatings (placement of a thin film of organic and inorganic osteoinductive and osteoproliferative materials) on implants surfaces increase osteoblastic activity thereby increasing bone volume (BV) and BIC under experimental

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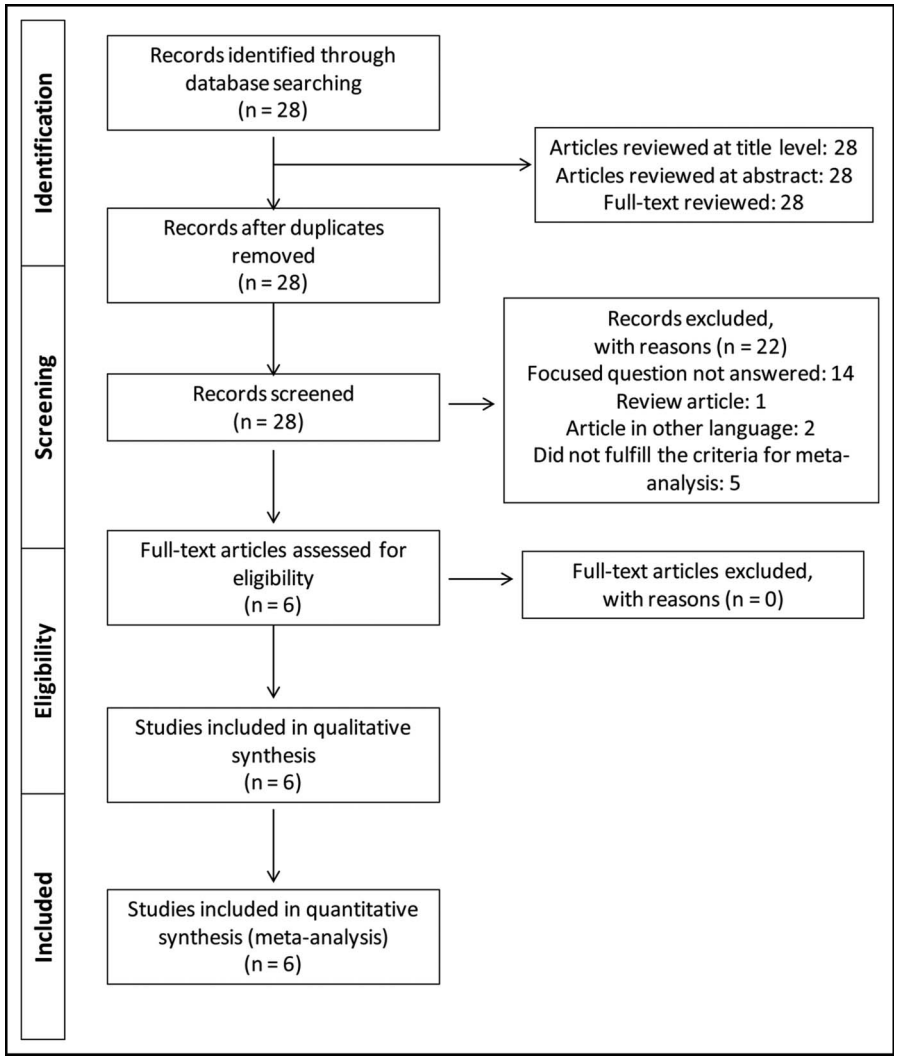

Fig. 1. Study selection protocol.

osteoporotic conditions in contrast to implants with noncoated surfaces. The aim of the present systematic review and meta-analysis was to assess the role of osteogenic coatings on implant surfaces in promoting BIC in experimental osteoporosis.

Methods and Materials

Focused Question

This systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] A specific question was constructed according to the Participants, Interventions, Control, and Outcomes (PICO) principle. The focused question was "Do osteogenic coatings on implant surfaces increase BIC in osteoporotic bone?"

(P) Participants: It was essential for the animals to have undergone implant treatment.

(I) Types of interventions: The intervention of interest was effect of osteogenic coatings on osseointegration in experimental osteoporosis.

(C) Control Intervention: Osseointegration without osteogenic coatings.

(O) Outcome Measures: BIC with and without osteogenic coatings.

Eligibility Criteria

The following eligibility criteria were entailed: (a) original studies; (b) experimental studies (animal models); (c) intervention: effect of osteogenic coatings on implant surfaces in promoting BIC in experimental osteoporosis; and (d) articles published only in English language. Letters to the Editor, commentaries, review articles, and case-reports/case-series were not sought.

Search Strategy

To address the focused question, PubMed/MEDLINE (National Library of Medicine, Bethesda, MD), EMBASE, Scopus, and Google-Scholar databases were searched up to and including June 2017 using the following key words: (a) bone-to-implant contact; (b) coating; (c) implant surface; (d) osseointegration; and (e) osteoporosis. These keywords were used in the following combinations: a + b + c + d + e, a + b + c + d, a + b + c, b + c + d + e, b + c + d, c + d + e, c + d, and d + e. Titles and abstracts of studies that fulfilled the eligibility criteria were independently screened by 2 authors (S.V.K. and F.J.) and checked for agreement. Full texts of studies judged by title and abstract to be relevant were read and independently assessed by the same authors (S.V.K. and F.J.) against the selection protocol. After this, reference lists of original and review studies that were found to be pertinent in the previous step were hand-searched. Any disagreement among the authors regarding study selection was resolved by discussion.

Meta-Analysis

Meta-analysis of mean differences was performed for %BIC between control and test groups on an animal level. By definition, a mean difference <0 indicated a greater effect size in the control group. In case of missing data for the meta-analysis, the corresponding author would be contacted for additional data. Heterogeneity among the included studies for each outcome was assessed using the Q-statistic and I^2 statistic.[21] Outcome measures were combined with a fixed-effects model unless significant heterogeneity among studies was found. In the case of heterogeneity, a random-effects model using the DerSimonian-Laird method was preferred.[22] Forest plots were produced reporting weighted mean differences and

95% confidence intervals. Sensitivity analysis was performed by removing outlier studies in terms of sample size (smallest) and effect size (largest) to assess the robustness of the results. The alpha level was set at a = 0.05. All above statistical analyses were performed by a specialized statistical software (R "metafor" package; R

Table 1. Characteristics of Experimental Studies Included

Authors et al	Subjects (Mean Age)	Study Groups	Implants Location	Implant Surface Modifications	Follow-up	Outcome
7	15 rats (3 mo)	Group-1: 15 OVX rats Group-2: 15 sham-operated rats	Femoral condyl	Implant-I: CaP coated Implant-II: collagen type-1 coated Implant-III: noncoated	12 wk	BV and BIC were significantly high around implant-I and implant-II than implant-III.
8	48 rats (NA)	Group-1: 64 OVX rats with simvastatin treatment Group-2: 32 OVX rats without simvastatin treatment.	Tibia	Group-1a: implants coated with 10^{-7} mol/L simvastatin Group-1b: implants coated with 10^{-6} mol/L simvastatin Group-2: implants without simvastatin coating	1, 2, 4 and 12 wk	In Groups 1a and 1b, new bone formation was seen after 1 wk and in Group-2 after 2 wk. At all time points, BV and BIC were significantly higher in Groups 1a and 1b than Group-2. There was no difference in BV and BIC in Groups-1a and 1b at all time points.
9	56 rabbits (NA)	Group-1: 40 OVX rabbits Group-2: 16 without OVX	Tibia	Group-1a: OVX alone Group-1b: local ZOL Group-1c: systemic ZOL Group-1d: local + systemic ZOL Group-2: sham surgery (controls)	12-wk	BV and BIC were significantly higher in groups 1b, 1c and 1d (with the highest increase occurring in group 1d) compared with group-2.
10	36 rabbits (6 mo)	Group-1: 12 OVX rabbits treated with alendronate-Na tablets Group-2: no treatment in 12 OVX rabbits Group-3: sham surgery (controls)	Parietal bones	In each group, 1 modSLA and 1 SLA titanium dome were placed.	4 and 16 wk	modSLA Ti surface significantly increased BIC and new bone formation in all groups compared with SLA surfaces.
11	20 rabbits (12 mo)	Group-1: 10 OVX rabbits Group-2: 10 rabbits without OVX	Tibia	In each group, implants with 3 types of surfaces were placed: (a) Ti implant (b) HA-PS implant (c) Implant coated with HA with biomimetic process	16-wk	There was no significant difference in BIC among the implants placed in groups 1 and 2.
12	40 rats	40 OVX rats	Tibia	Implants (n = 10/group) were immersed in 4 different solutions before placement: Group-a: water Group-b: ZOL Group-c: bFGF Group-d: ZOL + bFGF	12-wk	Compared with group-a, BV and BIC were significantly higher in groups b, c, and d. Highest BV and BIC were observed in group d compared with groups b and c.

alendronate-Na indicates alendronate-sodium; bFGF, basic fibroblast growth factor; CaP, calcium phosphate; HA, hydroxyapatite; HA-PS, hydroxyapatite coated and plasma sprayed; modSLA, modified-etched hydrophilic titanium; NA, not available; OVX, ovariectomized; SLA, etched titanium; SS, stainless steel; ZOL, zoledronate acid.

Table 2. Implant-Related Characteristics of the Studies Included

Authors et al	No. Implants Placed	Implant Shape	Implant Length (in mm)	Implant Diameter (in mm)	Implant Surface Characteristics
7	30 CaP or Collagen type-1 coated Ti implants 30 noncoated Ti implants	Cylindrical	5	2.85	Grit-blasted + CaP or collagen type-1 coating.
8	192	Screw-shaped	4	2.2	Grit-blasted + treated with hydrofluoric acid/nitric acid solution and hydrochloric acid/sulfuric acid solutions
9	80 Ti implants	Screw-shaped	12	2	HA and ZOL coating
10	72 Ti discs*	Screw-shaped	3*	5*	ModSLA and SLA
11	60 Ti implants	NA	10	3.8	HA-PS and HA with biomimetic process
12	20 Ti implants in distilled water 20 Ti implants in ZOL 20 Ti implants in bFGF 20 Ti implants in ZOL + bFGF	Cylindrical	12	1	HA immersed in water, ZOL, bFGF, or ZOL + bFGF

*Titanium disks were placed on induced parietal bone defects.
bFGF indicates basic fibroblast growth factor; CaP, calcium phosphate; HA, hydroxyapaptite; HA-PS, hydroxyapaptite coated and plasma sprayed; Ti, Titanium; ZOL, Zoledronate acid.

Development Core Team. 2010. URL: http://www.jstatsoft.org/v36/i03/).

RESULTS

Study Selection and General Characteristics

The initial search yielded 28 studies. Twenty-two studies, which did not fulfill the eligibility criteria, were excluded (Appendix A). In total, 6 studies[7–12] were included and processed for data extraction (Fig. 1).

General characteristics of the studies that were included in the present systematic review are shown in Table 1. All studies[7–12] were experimental and were performed at University settings. Rats and rabbits were used in 3[7,8,12] and 3[9–11] studies, respectively. Mean ages of rats and rabbits ranged between 3 to 10 months and 6 to 12 months, respectively. In all studies,[7–12] experimental osteoporosis was induced by bilateral ovariectomy. In the study by Mardas et al,[10] implants were placed in the parietal bone. In the remaining studies,[7–9,11,12] implants were either placed in the femoral condyle or tibia. The follow-up period ranged between 1 and 16 weeks.

Implant-Related Characteristics of the Studies

Implant-related characteristics of the studies[7–12] that fulfilled the eligibility criteria are shown in Table 2. In these studies,[7–12,23,24] the numbers of implants placed ranged between 30 and 192. In 2 studies,[7,12] cylindrical implants were used and screw-shaped implants were used in 3 studies.[8–10] In 1 study,[11] shape of the implants used was not reported. The lengths and diameters of implants used ranged between 3 to 12 mm and 1 to 5 mm, correspondingly. In all studies,[7–12] rough-surfaced dental implants were used. Calcium phosphate (CaP) and zoledronic acid (ZOL)-coated implant surfaces were used in 1[7] and 2 studies,[9,12] respectively; whereas 1 study[11] assessed the effect of using a duplex coating of hydroxyapatite on implant osseointegration under experimental osteoporotic conditions. In a study on rats,[12] effect of fibroblast growth factor with and without adjunct ZOL coating in increasing

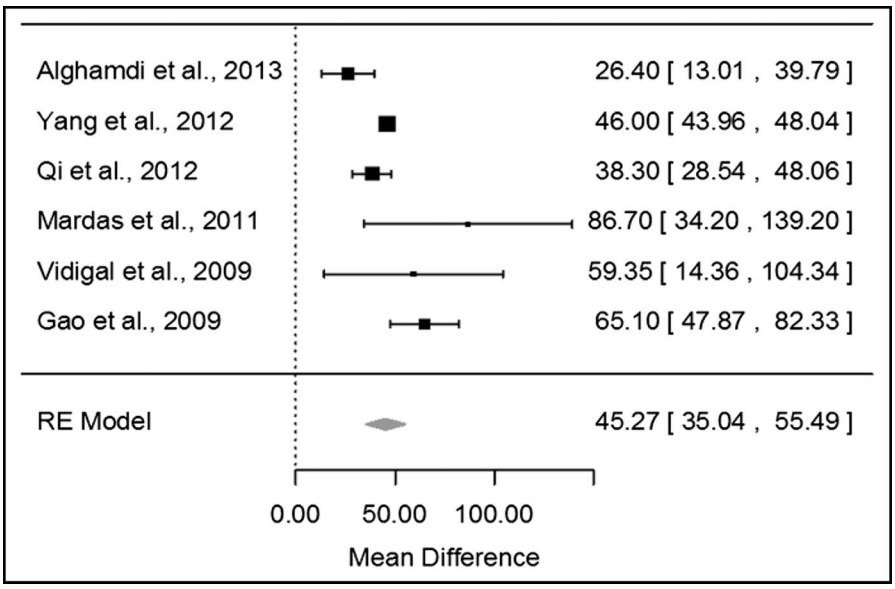

Fig. 2. Forest plot for included studies that reported %BIC in test implant surfaces versus conventional implant surfaces in medically compromised animals. The plot is showing weighted mean differences and 95% confidence intervals (95% CI). Weighted mean differences were estimated by a random-effects (RE) model.

BV and BIC was investigated; whereas in 1 study,[8] Ti implants were dipped in 2 different concentrations of a hypolipidemic drug before insertion in rat tibia.

Main Outcome of Studies

Results from 5 studies[7–10,12] showed that BV and BIC were significantly higher around implants with coated surfaces than noncoated implants. Results by Vidigal et al[11] showed no difference in BIC around coated and noncoated implants placed in animals with experimentally induced osteoporosis.

Meta-Analysis

Tests for heterogeneity demonstrated significant heterogeneity in the main meta-analysis ($Q = 17.83$, degrees of freedom $= 5$, P-value $= 0.003$, $I^2 = 71.95\%$) and the sensitivity analysis ($Q = 10.45$–13.26, $I^2 = 71.30\%$–77.38%), thus a random-effects model was used for all analyses. The pooled effect size for increase in %BIC was significant in favor of coated implants with a mean difference of 45.27% (35.04%, 55.49%), $P < 0.001$. After the exclusion of (1) Mardas et al[10] and Gao et al[12] that exhibited the largest effect size and (2) Mardas et al[10] and Qi et al[9] that had the smallest sample size, results remained similar with the mean difference in %BIC ranging between 39.57% and 46.20%, respectively ($P < 0.001$ in both cases) (Fig. 2).

DISCUSSION

In the present systematic review, only a limited number of studies fulfilled the eligibility criteria to be statistically assessed for a meta-analysis. Although this factor could be considered as a potential limitation of this study, yet the present results are based on the most recent evidence available. In general, studies[7–12] included in the present systematic review showed that implants with osteogenic coatings exhibited a higher BIC and BV in animals with experimentally induced osteoporosis than noncoated implants. An explanation in this regard may be derived from the fact that an increase in surface roughness of the implant (caused by osteogenic coatings) facilitates the attachment of osteoinductive cells to the implant surface. Studies[4,25,26] have also shown that long-term success of dental implants is related to the degree of primary stability (PS) achieved at the time of implant placement. It is therefore hypothesized that rough-surfaced implants promote bone formation around implants in systemically healthy and osteoporotic patients by enhancing the degree of PS as compared to implants with machined surfaces. It is noteworthy that all studies[7–12,23,24,27–29] included in this review were experimental and osteoporosis was induced in animals within 4 weeks to 24 months of ovariectomization.[7–12] From a clinical standpoint, it is well acknowledged that aging is a major risk factor of osteoporosis.[30] Therefore, it may be argued whether or not experimental osteoporosis induced in the experimental studies[7–12,23,24,27–29] included in the present review truly replicated a clinical scenario of osteoporosis. Moreover, it is known that hyperglycemia is commonly manifested in elderly osteoporotic patients.[31] Chronic hyperglycemia has been associated with an increased formation of advanced glycation end products (AGEs) and their accumulation in tissues including gingival tissues.[32] Increased interactions between AGEs and their receptors have been associated with increased gingival inflammation and alveolar bone loss (ABL).[33,34] It is well established that habitual use of tobacco in the form of smoking and smokeless tobacco products increases oral soft tissue inflammation and increases ABL.[35–39] Furthermore, the contribution of regular oral hygiene maintenance toward the preservation of periodontal and peri-implant soft- and hard-tissue status cannot be overlooked.[40] Because chronic hyperglycemia, advanced aging and habitual use of tobacco products undermine the differentiation and growth of osteoprogenitor cells[41–43]; it is hypothesized that the outcome of dental implant therapy in terms of maintenance of BIC is compromised in patients with poorly controlled diabetes, elderly individuals, and tobacco smokers in contrast to their corresponding controls (ie, systemically healthy subjects, younger individuals and individuals who have never used tobacco in any form, respectively). In this regard, merely using implants with osteogenic coatings in osteoporotic patients is most likely insufficient to promote BIC and enhance the long-term success and survival of dental implants.

A variety of implant coating materials were used in the studies and included in the present systematic review. For instance, Alghamdi et al[7] used CaP-coated implants and the results demonstrated that CaP coatings are effective in enhancing BIC and BV compared with noncoated implants. However, results by Qi et al[9] and Gao et al[12] showed that ZOL-coated implants augment osseointegration under experimental osteoporosis as compared to noncoated implant surfaces. Moreover, results by Gao et al[12] also reported that coating implant surfaces with growth factors with adjunct ZOL therapy increased BIC to a significantly greater extent as compared to when ZOL was used alone. CaP coatings increase the attachment of osteoblast-like cells and mesenchymal stem cells on implant surfaces[44]; and ZOL coatings improve osseointegration of hydroxyapatite-coated implants by converting the rod-like structure of trabeculae (following estrogen deficiency) to the plate-like structure thereby increasing bone mass around implants and improving implant fixation.[12] It is therefore difficult to nominate a specific implant coating material that may result in highest BIC under osteoporotic conditions. Furthermore, from the literature reviewed, it is difficult to determine the minimum thickness of the coating material (regardless of its composition) that would yield the most fruitful outcome in terms of augmenting BIC.

It has been reported that the secondary stability of implants is associated with the BIC and the role of implant diameter in this context is secondary.[45,46] From the literature reviewed, it was observed that although implants used in the respective studies varied in diameters (range 1–5 mm); histologic outcomes of most studies revealed significantly more BIC around coated implants than noncoated surfaces in animals with experimental osteoporosis. Further long-term randomized controlled clinical trials are warranted to assess

the impact of osteogenic coatings on osseointegration of dental implants in patients with osteoporosis.

CONCLUSION

On experimental grounds, osteogenic coatings on implant surfaces enhance BIC and seem to be a useful strategy for increasing the long-term success and survival of dental implants. However, from a clinical perspective, the role of osteogenic coatings on implant surfaces in terms of augmenting BIC remains debatable since several local and systemic factors influence BIC and not merely implant surface coatings. Further clinical trials are needed to assess the efficacy of osteogenic coatings on implant surfaces in augmenting osseointegration in osteoporotic patients.

DISCLOSURE

The authors claim to have no financial interest, either directly or indirectly, in the products or information listed in the article.

ROLES/CONTRIBUTION BY CO-AUTHORS

A. Ghanem: Wrote the abstract and introduction; S. V. Kellesarian and F. Javed: Performed the literature search and wrote the materials and methods; T. Abduljabbar, F. Vohra, and N. Al-Hamoudi: Wrote the results and fabricated the tables; F. Javed: Designed the study, wrote the discussion and revised the manuscript before submission.

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Appendix A. List of Excluded Studies. Reason for Exclusion is Shown in Parenthesis

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