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REVIEW ARTICLE



# Effect of local zoledronate delivery on osseointegration: a systematic review of preclinical studies

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**ABSTRACT**

**Purpose:** The aim of the present systematic review was to assess the effect of local zoledronate (ZOL) delivery (topical or as implant surface coatings) on osseointegration.

**Materials and methods:** In this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. To address the focused question, 'Does local zoledronate delivery enhance osseointegration?' indexed databases were searched without time or language restrictions up to and including April 2017 using various combination of the following keywords: 'zoledronate', 'bisphosphonates', 'osseointegration' and 'topical administration'. Letters to the Editor, historic reviews, commentaries, case-series and case-reports were excluded.

**Results:** Initially, 383 articles were identified out of which, 23 experimental studies fulfilled the inclusion criteria. In 18 studies, ZOL was incorporated into implants surfaces as a coating and in five studies ZOL was applied topically (bone graft or irrigation) into the bone cavities. Results from 87% studies reported that local delivery of ZOL (coating or topical) is effective in enhancing osseointegration or new bone formation around implants.

**Conclusions:** Local ZOL delivery (coating or topical) seems to enhance osseointegration in animals; however, from a clinical perspective, further randomized control trials with long-term follow-up are needed in this regard.

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Bisphosphonates; implants; osseointegration; topical administration; zoledronate

## Introduction

Dental implants are a modern and reliable treatment option for the replacement of missing teeth in partially and totally edentulous patients [1,2]. It is well-known that achievement of primary stability at the time of implant placement and use of implants with moderately rough surfaces (compared with implants with machined surfaces) are essential parameters that help in the formation of a direct bone-to-implant contact (BIC) thereby influencing the overall success and survival of dental implant therapy [3,4]. However, additional therapies such as parathyroid hormone and vitamin D supplementation and antiresorptives delivery have also been shown to facilitate osseointegration [5–9].

Bisphosphonates (BPs) are stable pyrophosphate analogues that modulate bone metabolism, and are commonly used in the treatment of resorptive skeletal disorders, including osteoporosis, Paget's disease and bone metastasis [10,11]. BPs are classified into two types: (a) non-nitrogen containing (such as, clodronate and etidronate) and (b) nitrogen-containing BPs (such as pamidronate, alendronate, risedronate, ibandronate and zoledronate [ZOL]). The incorporation of nitrogen into their chemical structure potentiates the inhibition of bone resorption acting in the enzyme farnesyl pyrophosphate synthase, thereby suppressing osteoclast activity and promoting an anabolic effect towards enhancing new bone formation (NBF) [12–15]. Important differences exist between individual BPs in terms of potency, onset and duration of action, and clinical effectiveness [13]. ZOL, which contains a nitrogen atom within heterocyclic rings is intrinsically more potent inhibiting bone resorption compared to other BPs. ZOL anabolic–catabolic properties have been studied *in vitro*, reporting enhanced osteoblastic proliferation and decreased osteoclastic formation and resorptive activity [16].

Studies [17–39] have investigated the role of local ZOL delivery (topical or in the form of implant surface coatings) on the osseointegration and NBF around implants. In a study on dogs, Cuairan et al. [21] reported increased trabecular NBF and stability around miniscrew titanium (Ti) implants placed in the maxilla and mandible after ZOL intra-cavity irrigation for 60 seconds. In a study on sheep with experimentally-induced osteoporosis, Stadelmann et al. [29] reported higher bone area (BA) around Ti implants coated with hydroxyapatite and ZOL compared with hydroxyapatite coating alone. Similar results were reported by Roshan-Ghias et al. [36] and Gao et al. [32]. However, conflicting results have been also reported. Arnoldi et al. [19] reported no

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Supplemental data for this article can be accessed here.

statistically significant difference in BIC and NBF among Ti implants with or without ZOL coatings. Likewise, Jakobsen et al. [22] also reported no statistically significant difference in comparable amounts of BIC and NBF around Ti implants with beta-tricalcium phosphate (β-TCP) bone graft granules without ZOL.

With this background, the efficacy of ZOL local delivery in terms of improving osseointegration seems to be debatable. Therefore, the aim of the present systematic review was to assess the effect of local ZOL delivery (topical or the form of implant surface coatings) on the osseointegration.

## Materials and methods

### Focused question

This systematic review was conducted by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40]. According to the Participants, Interventions, Control, Outcomes (PICO) principle, the addressed focused question was 'Does local zoledronate delivery enhances osseointegration around implants?'

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

(I) Types of interventions: The intervention of interest was local delivery of ZOL on osseointegration.

(C) Control intervention: Implant placement without adjunct local ZOL administration.

(O) Outcome measures: BIC, NBF, bone volume/tissue volume (BV/TV) and/or biomechanical fixation around implants with and without local ZOL delivery.

### Eligibility criteria

The eligibility criteria were as follows: (a) original clinical and animal/experimental studies; (b) presence of a control group (osseointegration around implants without local ZOL delivery); (c) intervention: effect of local ZOL (topical or coating) on osseointegration. Laboratory-based investigations (*in vitro* studies), letters to the Editor, historic reviews, commentaries, case-series and case-reports were excluded. Articles available online in electronic form ahead of print were considered eligible for inclusion.

### Information sources, literature search strategy and study selection

An electronic search without time or language restrictions was conducted up to and including April 2017 in PubMed (National Library of Medicine), Scopus, EMBASE, MEDLINE (OVID) and Web of Knowledge databases, in order to identify studies relevant to the focused question. Search term included Medical subject headings (MeSH) and text words (other relevant non-MeSH terms) to identify articles discussing osseointegration parameters and/or ZOL administration. These included the following MeSH terms: (1) zoledronate; (2) bisphosphonates; (3) topical administration; and (4) osseointegration; and text words: (5) local delivery; (6) local administration; (7) coating; (8) coated; (9) bone-to-implant contact; (10) new bone formation and (11) implants. These keywords were used with Boolean operators (OR, AND) to combine the keywords mentioned above. For each aforementioned database, the following search strategy was used: (zoledronate [MeSH] OR bisphosphonates [MeSH]) AND (topical administration [MeSH] OR local delivery OR local administration) AND (osseointegration [MeSH] OR bone-to-implant contact OR new bone formation); (zoledronate [MeSH] OR bisphosphonates [MeSH]) AND (coating OR coated) AND (implants); (zoledronate [MeSH] OR bisphosphonates [MeSH]) AND (osseointegration [MeSH]) AND (coating OR coated) AND (implants).

Titles and abstracts of studies identified using the above-described protocol were screened by two authors (SVK and FJ) and checked for agreement. Full-texts of studies judged by their titles and abstracts to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify studies that have remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. Kappa scores (Cohen's kappa coefficient) were used to determine the level of agreement between the two reviewers (Kappa score = 0.88) [41].

### Quality assessment

In an attempt to increase the strength of the present systematic review, the selected studies underwent a quality assessment following the Animal Research Reporting in Vivo Experiment (ARRIVE) guidelines [42–44] and to a pre-defined grading [45,46] applied to the following 20 specific criteria: (1) Title (concise and accurate); (2) Abstract (summary of background, objectives, methods, main findings and conclusions); (3) Introduction (background objectives, relevance to human biology); (4) Introduction (primary and secondary objectives); (5) Methods (Ethical statement, national and institutional guidelines for the care and use of animals); (6) Methods (study design, steps taken to minimize bias such as allocation concealment, blinding and randomization); (7) Methods (experimental procedure with precise details); (8) Methods (experimental animals details including species, gender, age, weight and source); (9) Methods (housing and husbandry conditions such as, type of cage, light/dark cycle, temperature, access to food and water); (10) Methods (sample size); (11) Methods (allocation of animals to experimental groups, randomization); (12) Methods (experiment outcomes); (13) Methods (statistical analysis); (14) Results (baseline data, health status of animals); (15) Results (number of animals analysed, reasons for exclusion); (16) Results (outcomes and estimation, results for each analysis); (17) Results (adverse events); (18) Discussion (interpretation, scientific implications, study limitations including animal model); (19) Discussion (generalizability and translation, relevance to human biology); and (20) Discussion (funding sources, role of the funders, conflicts of interest).

Each criterion was given a grade following ARRIVE guidelines and recommendations reported previously [42,45]. Briefly, items 1, 4, 11 and 14 could have a minimum grade of 0 and a maximum grade of 1 (0 = inaccurate, not concise or not reported; 1 = accurate, concise or reported). Whereas, items 2, 3, 5, 6, 7, 8, 9, 10, 12, 13, 15, 16, 17, 18, 19 and 20 could have a minimum grade of 0 and a maximum grade of 2 (0 = clearly inaccurate or not reported; 1 = possibly accurate, unclear or incomplete; 2 = clearly accurate). Maximum score by columns (1–20) were totalized to obtain the quality score by category. According to this, a relationship quality score/maximum score generated three possible quality coefficients: excellent (0.8–1), average (0.5–0.8) and poor (<0.5).

Quality assessment of studies included was conducted independently by two authors (SVK and FJ) using the above-described tool, and checked for disagreement via discussion among the authors (Kappa score =0.76).

## Results

### Study selection

Three hundred and eighty-three potential articles were initially identified. In the first step, 319 publications which did not answer the focused question or were duplicates were excluded. In the next step, 41 more articles were excluded (Supplementary Appendix). A total of 23 studies [17–39] were included in the present systematic review and processed for data extraction. Figure 1 summarizes the literature search strategies according to the PRISMA guidelines. In order to minimize the heterogeneity among the studies included, the results were grouped and reported per animal species.

### General characteristics

Tables 1 and 2 summarize the general characteristics of the studies included in the present systematic review.

### Studies in rats

Twelve studies [17,18,20,25–27,30–33,35,38] were performed in rats. Eight studies [20,25–27,31,32,35,38] were performed in female rodents, three studies [17,18,30] in male rats, and in one study [33] the gender was not reported. In all studies [17,18,20,25–27,30–33,35,38], ZOL was delivered locally, out of which in one study [38] ZOL was topically applied into bone cavities, and in 11 studies [17,18,20,25–27,30–33,35] ZOL-coated implants were used. In five [25,26,30–32] and two studies [20,33], ZOL was incorporated into hydroxyapatite and poly-D,L-lactide (PDLLA) coated implants, respectively. In two studies [17,18], implants were coated with a fibrinogen matrix into which ZOL was incorporated. Pyo et al. [27] assessed NBF around implants coated with calcium phosphate (CaP) and ZOL. In all studies [17,18,20,25–27,30–33,35,38], the follow-up period ranged between 2 weeks and 24 weeks. In seven studies [17,18,20,25,26,30,33], role of ZOL in the promotion of NBF around implants was assessed in healthy rodents; whereas, in five studies [27,31,32,35,38], the effectiveness of ZOL on implants osseointegration was assessed in rats with induced osteoporosis; Suratwala et al. [30] injected ultra-high

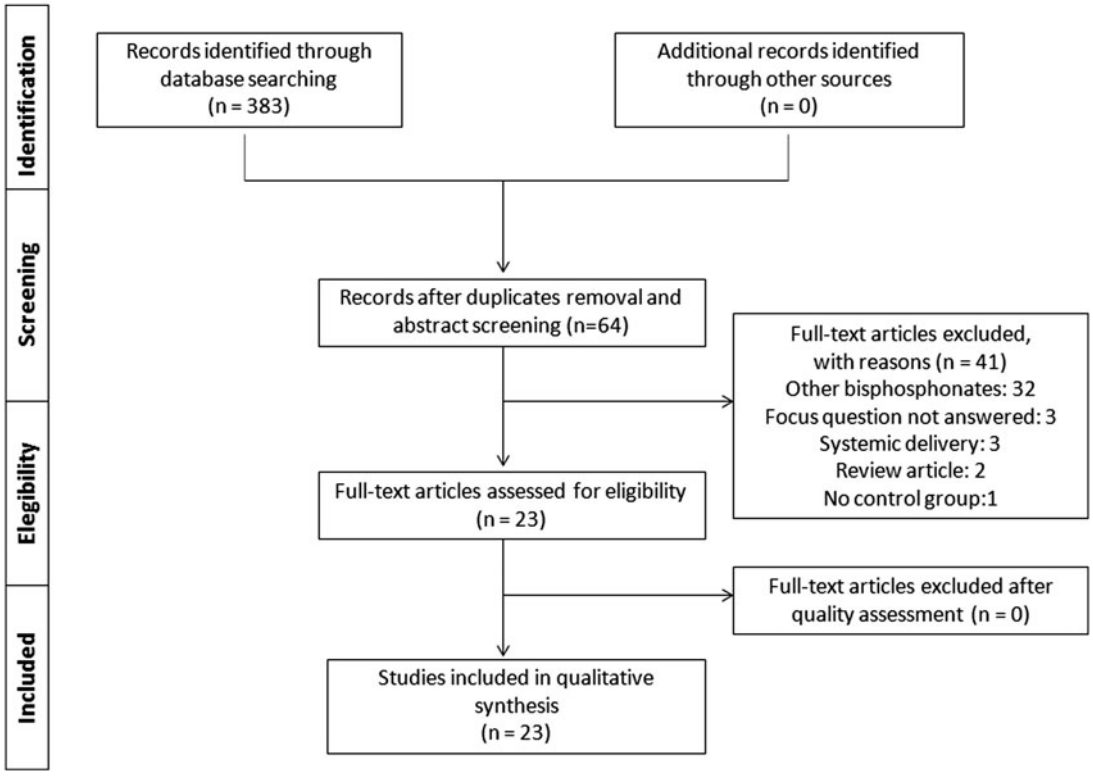


**Figure 1.** Article selection flowchart for the systematic review according to PRISMA guidelines.

**Table 1.** Studies with zoledronate-coated surfaces.

| Authors | Study subjects (mean age) | Study groups | Bisphosphonates dose and route of administration | Follow-up (weeks) | Analysis methods | Outcome |
|---|---|---|---|---|---|---|
| *Studies in rats* | | | | | | |
| Abtahi et al. [17] | 40 Male (2.2-month-old) | Group 1: Control<br>Group 2: SQ DEX<br>Group 3: SQ DEX + ALE<br>Group 4: SQ DEX + ZOL solution + FIB | Group 3: Systemic ALE 200 μg/kg ×14 days<br>Group 4: ZOL solution 400 ng + FIB | Up to 2 | Removal torque<br>Micro-CT | Group 4 presented higher implant removal torque, BV/TV and NBF compared with groups 1, 2 and 3. |
| Andersson et al. [18] | 109 Male (2- to 2.2-month-old) | Group 1: PAM + FIB<br>Group 2: ZOL + FIB<br>Group 3: FIB<br>Group 4: Uncoated SS | Group 1: PAM solution 1 mg/ml, 279 ng/cm$^2$<br>Group 2: ZOL solution 15 mg/ml, 108 ng/cm$^2$ | Up to 6 | Pull-out test<br>HIST | Group 2 presented higher BMD and strength of fixation compared with groups 1, 3 and 4. |
| Back et al. [20] | 100 Female (5-month-old) | Group 1: Uncoated K-wire<br>Group 2: PDLLA<br>Group 3: PDLLA + ZOL 20 μg<br>Group 4: PDLLA + ZOL 50 μg<br>Group 5: Uncoated K-wire + ZOL IV | ZOL<br>Group 3: 20 μg<br>Group 4: 50 μg<br>Group 5: 0.1 mg/kg IV | Up to 8 | Radiographs<br>Push-out test<br>HIST | No significant difference between groups 3 and 4 compared with groups 1 and 2 in terms of BIC, NBF and strength of fixation. |
| Gao et al. [31] | 40 Female (NA) | Group 1: OVX + HA<br>Group 2: OVX + HA + ZOL<br>Group 3: OVX + HA + bFGF<br>Group 4: OVX + HA + ZOL + bFGF | Group 2: ZOL solution 1 mg/ml<br>Group 3: ZOL solution 1mg/ml and bFGF 20 μg/ml | Up to 12 | Histology<br>HIST<br>Micro-CT<br>Push-out test | Group 4 presented significantly higher BA, BIC and strength of fixation compared with groups 1, 2 and 3. No significant difference in BIC between groups 2 and 3. |
| Gao et al. [32] | 40 Female (NA) | Group 1: OVX + HA<br>Group 2: OVX + HA + PAM<br>Group 3: OVX + HA + IBA<br>Group 4: OVX + HA + ZOL | Group 4: ZOL solution 1 mg/ml | Up to 12 | DEXA<br>Micro-CT<br>HIST<br>Push-out test | Group 4 presented higher BIC, BV/TV, NBF and strength of fixation compared with groups 1, 2 and 3. |
| Greiner et al. [33] | 49 (5-month-old) | Group 1: Uncoated Ti<br>Group 2: Ti + PDLLA<br>Group 3: Ti + PDLLA + ZOL | Group 3: ZOL solution 50 μM, 20 μg per implant | Up to 12 | Radiographs<br>Push-out test | Group 3 presented higher maximum load and torsional stiffness compared with groups 1 and 2. |
| Peter et al. [26] | 20 Female (6-month-old) | Group 1: HA<br>Group 2: HA + ZOL 0.2 μg<br>Group 3: HA + ZOL 2.1 μg<br>Group 4: HA + ZOL 8.5 μg<br>Group 5: HA + ZOL 16 μg | ZOL solution<br>Group 2: 0.2 μg<br>Group 3: 2.1 μg<br>Group 4: 8.5 μg<br>Group 5: 16 μg | Up to 3 | HIST<br>SEM<br>Pull-out test | Group 3 presented higher pullout force compared with groups 1, 2, 4 and 5. |
| Peter et al. [25] | 25 Female (6-month-old) | Group 1: HA<br>Group 2: HA + ZOL 0.2 μg<br>Group 3: HA + ZOL 2.1 μg<br>Group 4: HA + ZOL 8.5 μg<br>Group 5: HA + ZOL 16 μg | ZOL solution<br>Group 2: 0.2 μg<br>Group 3: 2.1 μg<br>Group 4: 8.5 μg<br>Group 5: 16 μg | Up to 3 | SEM<br>HIST<br>Micro-CT<br>Pull-out test | Group 4 presented higher pullout force compared with groups 1, 2, 3 and 5. Group 1 presented lower BVF compared with the rest of the groups. |
| Pyo et al. [27] | 20 Female (2-month-old) | Group 1: OVX + CaP<br>Group 2: OVX + CaP + ZOL 8 μg<br>Group 3: OVX + CaP + ZOL 80 μg<br>Group 4: OVX + CaP + ZOL 800 μg | ZOL<br>Group 2: 8 μg<br>Group 3: 80 μg<br>Group 4: 800 μg | Up to 8 | Histology<br>HIST<br>Micro-CT | Group 4 presented significantly higher BV/TV compared with groups 1, 2 and 3. No significant difference in BIC among groups. |
| Stadlinger et al. [35] | 224 Female (6-month-old) | Group 1: Sham<br>Group 2: | Group 7: ZOL 8.5 μg | Up to 4 | HIST<br>Micro-CT | Group 7 presented a significant increase in BIC, BA, |

(*continued*)

**Table 1.** Continued

| Authors | Study subjects (mean age) | Study groups | Bisphosphonates dose and route of administration | Follow-up (weeks) | Analysis methods | Outcome |
|---|---|---|---|---|---|---|
| | | Sham + conditioned implant<br>Group 3: OVX<br>Group 4: OVX + conditioned implant<br>Group 5: OVX + collagen<br>Group 6: OVX + simvastatin<br>Group 7: OVX + ZOL | | | Removal torque | BV/TV and BMD compared with groups 3, 4, 5 and 6. No significant difference in biomechanical properties. |
| Suratwala et al. [30] | 32 Male (6-month-old) | Group 1: HA + IPP<br>Group 2: HA + IPP + ZOL | Group 2: ZOL 50 μM | Up to 24 | DEXA<br>Micro-CT<br>Pull-out test | Group 2 presented higher strength of fixation and BMD compared with group 1. No significant difference in BA between groups 1 and 2. |
| *Studies in rabbits* | | | | | | |
| Arnoldi et al. [19] | 12 Male (NA) | Group 1:Uncoated Ti<br>Group 2: FIB + ZOL | Group 2: ZOL 150 ng/cm$^2$ | Up to 1.5 | Radiographs<br>Histology<br>HIST | No significant difference in NBF and BIC between groups 1 and 2. |
| Qi et al. [28] | 56 Female (NA) | Group 1: Sham<br>Group 2: OVX + HA<br>Group 3: OVX + HA + ZOL local<br>Group 4: OVX + HA + ZOL SQ<br>Group 5: OVX + HA + ZOL local and SQ | ZOL<br>Group 3: 1 mg/ml solution<br>Group 4: 0.1 mg/kg SQ<br>Group 5: 1 mg/ml solution and 0.1 mg/kg SQ | Up to 12 | Micro-CT<br>Histology<br>Removal Torque<br>DEXA | Group 5 presented significantly higher BIC, BV/TV, BMD and removal torque compared with the other groups.<br>Group 3 presented significant higher BV/TV and BIC compared with group 2. |
| Roshan-Ghias et al. [36] | 48 (4-month-old) | Group 1: FIB + ZOL<br>Group 2: Uncoated Ti | Group 1: ZOL solution 150 ng/cm$^2$ | Up to 11 | Micro-CT<br>Histology<br>Pull-out test | Group 1 presented higher BVF, BMD and pullout force compared with group 2. |
| *Studies in dogs* | | | | | | |
| Jakobsen et al. [23] | 10 Female (NA) | Group 1: Uncoated Ti<br>Group 2: ZOL + PDLLA | Group 2: ZOL solution 0.02 mg | Up to 12 | HIST<br>Push-out test | Group 2 presented higher biomechanical fixation and BVF compared with group 1. |
| Jakobsen et al. [24] | 10 Female (NA) | Group 1: HA<br>Group 2: HA + ZOL + PDLLA | Group 2: ZOL solution 0.02 mg | Up to 12 | HIST<br>Push-out test | Group 2 presented higher biomechanical fixation, BVF and NBF compared with group 1. No significant difference in BIC. |
| Tanzer et al. [34] | 9 (NA) | Group 1: HA<br>Group 2: HA + ZOL<br>Group 3: Uncoated Ta<br>Group 4: Ta + ZOL | Groups 2 and 4: ZOL 0.05 mg | Up to 12 | SEM<br>Histology | Groups 2 and 4 presented higher BIC and NBF compared with groups 1 and 3. |
| *Studies in sheep* | | | | | | |
| Stadelmann et al. [29] | 3 Female (NA) | Group 1: OVX + HA<br>Group 2: OVX + HA + ZOL | Group 2: ZOL solution $2.25 \times 10^{-5}$ mol L$^{-1}$ (2.1 μg per implant) | Up to 4 | SEM | Group 2 presented higher BA compared with group 1. |

SQ: subcutaneous; DEX: dexamethasone; ALE: alendronate; ZOL: zoledronate; FIB: fibrinogen; MicroCT: microcomputer tomography; BV/TV: bone volume/tissue volume; NBF: new bone formation; PAM: pamidronate; SS: stainless steel; HIST: histomorphometry; BMD: bone mineral density; K-wire: Kirschner wire; PDLLA: poly-(D,L-lactide); IV: intravenous; BIC: bone-to-implant contact; ; OVX: ovariectomized; HA: hydroxyapatite; bGFG: basic fibroblast growth factor; BA: bone area; IBA: ibandronate; DEXA: dual energy X-ray absorptionmetry; Ti: titanium; SEM: scanning electron microscope; BVF: bone volume fraction; CaP: calcium phosphate; IPP: injected polyethylene particles; Ta: tantalum; NA: not available.

**Table 2.** Studies with topical delivery of zoledronate.

| Authors | Study subjects (mean age) | Study groups | Bisphosphonates dose and route of administration | Follow-up (weeks) | Analysis methods | Outcome |
|---|---|---|---|---|---|---|
| *Studies in rats* | | | | | | |
| Ying et al. [38] | 20 Female (NA) | Group 1: OVX + SAL<br>Group 2: OVX + ZOL | 30 µl ZOL (1 mg/ml)<br>Intra cavity injection | Up to 12 | DEXA<br>Histology<br>Micro-CT | Group 2 presented higher BIC, BA, BMD compared with group 1. |
| *Studies in rabbits* | | | | | | |
| Dundar et al. [37] | 12 Female (10- to 12-month-old) | Group 1: Ti CB<br>Group 2: Ti SLA<br>Group 3: Ti CB + ZOL local<br>Group 4: Ti SLA + ZOL local<br>Group 5: Ti CB + systemic ZOL<br>Group 6: Ti SLA + systemic ZOL | Groups 3 and 4: 1 ml of SAL with 2 mg ZOL<br>Intra cavity injection | Up to 4 | HIST<br>Histology | Groups 3 and 4 presented higher BIC compared with groups 1 and 2, but no superior to groups 5 and 6. |
| *Studies performed in dogs* | | | | | | |
| Baas et al. [39] | 10 Female (13- to 15-month-old) | Group 1: Allograft<br>Group 2: Allograft + BMP2<br>Group 3: Allograft + ZOL<br>Group 4: | Allograft + BMP2 - + ZOL | Groups 2 and 4: Allograft soaked in 1 ml ZOL solution (0.005 mg/ml ZOL) | Up to 4 | Histology<br>Push-out test<br>Group 3 presented higher strength of fixation compared with groups 1, 2 and 4. No significant difference in NBF among groups. |
| Cuairan et al. [21] | 3 Male (12- to 24-month-old) | Group 1: SAL<br>Group 2: SAL + ZOL | 16 µg ZOL<br>Intra cavity injection | Up to 8 | Resonance frequency analysis<br>Micro-CT | Group 2 was significantly more stable and presented more trabecular NBF compared with group 1. |
| Jakobsen et al. [22] | 10 Female (NA) | Group 1: β-TCP graft + SAL<br>Group 2: β-TCP graft + ZOL | β-TCP bone graft granules soaked in 1 ml ZOL solution (0.05 mg ZOL) | Up to 12 | Push-out test<br>HIST | Group 2 presented significantly higher maximum shear stiffness, compared with group 1. No significant difference in NBF and BIC. |

NA: not available; OVX: ovariectomized; SAL: saline; ZOL: zoledronate; DEXA: dual energy X-ray absorptionmetry; MicroCT: microcomputer tomography; BIC: bone-to-implant contact; BA: bone area; BMD: bone mineral density; Ti: titanium; CB: ceramic blasted; SLA: sandblasted large acid-grit; HIST: histomorphometry; BMP2: bone morphogenetic protein 2; NBF: new bone formation; β-TCP: beta-tricalcium phosphate.

**Table 3.** Characteristics of the implants included in all studies.

| Authors | Number and material of implants | Implant dimensions ($D \times L$ in mm) | Location of implant placement | Implant shape | Implant surface characteristics |
|---|---|---|---|---|---|
| Studies in rats | | | | | |
| Abtahi et al. [17] | 40 Ti | 1.5 × 3 | Maxilla | Screw | NA |
| Andersson et al. [18] | 109 SS | 1.7 × 3 | Tibia | Screw | Rough |
| Back et al. [20] | Ti K-wire | 1.4 × NA | Femur | Wire | Smooth |
| Gao et al. [31] | 80 Ti | 1 × 12 | Tibia | Cylinder | Rough (HA) |
| Gao et al. [32] | 80 Ti | 1 × 10 | Tibia | Cylinder | Rough (HA) |
| Greiner et al. [33] | Ti K-wire | 1 × NA | Tibia | Wire | Smooth |
| Peter et al. [26] | Ti (NA) | 3 × 5 | Femur | Cylinder | Rough (HA) |
| Peter et al. [25] | Ti (NA) | 3 × 5 | Femur | Cylinder | Rough (HA) |
| Pyo et al. [27] | 40 Ti | 1.2 × 3 | Tibia | Screw | Rough |
| Stadlinger et al. [35] | Ti (NA) | 1.7 × 3 | Tibia | Screw | Rough |
| Suratwala et al. [30] | SS and polyethylene (NA) | 1.4 × 20 | Femur | Nail | Rough (HA) |
| Ying et al. [38] | 20 Ti | 1 × 10 | Tibia | Cylinder | NA |
| Studies in rabbits | | | | | |
| Arnoldi et al. [19] | 24 Ti | 4 × 14 | Femur | Screw | Rough |
| Dundar et al. [37] | 48 Ti | 3 × 6 | Tibia | Screw | Rough |
| Qi et al. [28] | Ti (NA) | 2 × 12 | Tibia | Screw | Rough (HA) |
| Roshan-Ghias et al. [36] | Ti (NA) | 4 × 14 | Femur | Screw | Smooth |
| Studies in dogs | | | | | |
| Baas et al. [39] | 40 Ti | 6 × 10 | Femur | Cylinder Gap model | Rough (HA) |
| Cuairan et al. [21] | 60 Ti | 1.6 × 5 | Mandible and maxilla | Screw | NA |
| Jakobsen et al. [22] | 20 Ti | 6 × 10 | Tibia | Cylinder Gap model | Rough |
| Jakobsen et al. [23] | 20 Ti | 6 × 10 | Tibia | Cylinder press-fit | Rough |
| Jakobsen et al. [24] | 20 Ti | 6 × 10 | Tibia | Cylinder press-fit | Rough (HA) |
| Tanzer et al. [34] | Ta (NA) | 5 × 50 | Ulna | Cylinder | Rough (HA) |
| Studies in sheep | | | | | |
| Stadelmann et al. [29] | 6 Ti | 3 × 5 | Femur | Cylinder | Rough (HA) |

Ti: titanium; Ta: tantalum; SS: stainless steel; HA: hydroxyapatite; *D*: diameter; *L*: longitude; K-wire: Kirschner wire; NA: not available.

molecular weight polyethylene particles into rats' femora before implantation to stimulate a wear debris reaction.

### *Studies in rabbits*

Four studies [19,28,36,37] assessed the role of local ZOL delivery on implant osseointegration in rabbits. In one study [19], male rabbits were used, in two studies [28,37] female rabbits were used, and in the study by Roshan-Ghias et al. [36] the gender of rabbits remained unclear. Three studies [19,36,37] were performed in systemically healthy rabbits; whereas, in the study by Qi et al. [28], ovariectomized rabbits were used. Implants coated with ZOL were used in three studies [19,28,36], out of which, in two studies [19,36] ZOL was incorporated into a fibrinogen matrix and in hydroxyapatite in one study [28]. In one study [37], bone cavities were irrigated with ZOL before implantation. The follow-up period among the studies [19,28,36,37] ranged between 1.5 weeks and 12 weeks.

### *Studies in dogs*

Six studies [21–24,34,39] were conducted in systemically healthy dogs. Female and male dogs were used in four studies [22–24,39] and one study [21], respectively. In one study [34], dog's gender was not reported. Three studies [23,24,34] used implants coated with ZOL. Jakobsen et al. [23,24] incorporated ZOL into a PDLLA matrix, whereas, Tanzer et al. [34] used hydroxyapatite to fixate ZOL. Two studies [22,39] investigated the effects of bone grafts (β-TCP granules or allograft) soaked in 1 ml ZOL solution packed in a 2.5 mm gap around implants placed in dogs' tibiae or femur to improve implant and biomechanical fixation. Cuairan et al. [21] injected ZOL solution into the bone cavity previous implant placement to evaluate it effectiveness in the improvement of osseointegration. In all studies [21–24,34,39], the follow-up period ranged between 4 weeks and 12 weeks.

### *Studies in sheep*

Stadelmann et al. [29] studied the effect of Ti implants coated with hydroxyapatite and ZOL on peri-implant bone after 4 weeks of implantation in an osteoporotic sheep model.

## *Implant-related characteristics*

Table 3 summarizes the characteristics of the implants included in the present systematic review.

### *Studies in rats*

In eight studies [17,25–27,31,32,35,38], Ti implants were used. Back et al. [20] and Greiner et al. [33] implanted Ti Kirschner wires (K-wires) with 1.4 mm and 1 mm diameter, respectively. Andersson et al. [18] placed stainless steel (SS) screws, whereas, Suratwala et al. [30] assessed osseointegration around polyethylene implants and SS nails. Six studies [17,18,27,31,32,38] reported the total numbers of implants placed in the subjects, which ranged between 20 and 109 implants. In six studies [20,25,26,30,33,35], the total number of implants placed was not reported. Implant dimensions was reported in all the studies which ranged between 1 and 6 mm in diameter and 3–20 mm in length. In seven studies [18,27,31–33,35,38] and four studies [20,25,26,30], implants

were placed in tibia and femur, respectively. Abtahi et al. [17] used a rat's maxilla model.

### Studies in rabbits

Four studies [19,28,36,37] placed screw Ti implants in rabbit's tibiae and femur. Arnoldi et al. [19] and Dundar et al. [37] used 24 and 48 implants, respectively. In two studies [19,37], the total number of implants placed was not reported. Implant dimensions (diameter × length) were reported in all the studies [19,28,36,37], which ranged between 2 × 12 mm and 4 × 14 mm.

### Studies in dogs

In five studies [21–24,39], between 20 and 60 Ti implants were used. Tanzer et al. [34] studied NBF around Tantalum implants placed in dog's ulna. Implant dimensions were reported in all the studies [21–24,34,39] which ranged between 1.6 and 6 mm in diameter and 5–50 mm in length. In three studies [22–24] and one study [39], implants were placed in tibia and femur, respectively. Cuairan et al. [21] used a dog's maxilla and mandible model.

### Studies in sheep

Stadelmann et al. [29] assessed osseointegration around six Ti cylindrical implants (dimension 3 × 5 mm) in sheep's femur.

## Main outcomes

### Studies in rats

*Topical delivery of ZOL*. One study [38] reported higher BIC, BA and bone mineral density (BMD) around Ti implants placed after ZOL intra cavity injection.

*Implants with ZOL-coated surfaces*. Results from eight studies [17,18,25,26,30–33] reported improved biomechanical properties around implants coated with ZOL compared with implants without ZOL incorporation. However, Back et al. [20] and Stadlinger et al. [35] reported no significant difference in the strength of fixation around Ti K-wire and implants coated with ZOL compared with controls, respectively. In eight studies [17,18,25,27,30–32,35], ZOL incorporation improved NBF, bone volume fraction (BVF) and/or BIC. One study [20] reported no significant difference in terms of NBF between uncoated Ti implants and ZOL coated Ti implants. In two studies [20,27], comparable BIC values between implants with and without ZOL coating were reported.

### Studies in rabbits

*Topical delivery of ZOL*. Dundar et al. [37] reported higher BIC around implants placed after ZOL intra-cavity injection compared with control group (saline solution).

*Implants with ZOL-coated surfaces*. Roshan-Ghias et al. [36] reported improved biomechanical properties around implants coated with fibrinogen and ZOL compared with uncoated implants. Qi et al. [28] showed that ZOL incorporated in a hydroxyapatite matrix improved BV/TV and BIC around implants. Arnoldi et al. [19] reported no significant difference in terms of NBF between uncoated Ti implants and ZOL coated Ti implants.

### Studies in dogs

*Topical delivery of ZOL*. Cuairan et al. [21] reported higher BIC, BA and/or BMD around Ti implants placed after ZOL intra cavity injection. Baas et al. [39] reported improved strength of fixation but no difference in NBF around implants placed around allograft bone soaked in ZOL solution. Jakobsen et al. [22] reported increased maximum shear stiffness, but no difference in maximum shear strength, total energy absorption and NBF around implants grafted with β-TCP granules soaked in ZOL compared with control group.

*Implants with ZOL-coated surfaces*. Two studies [23,24] reported higher strength of fixation and BVF around implants coated with ZOL compared with controls. Two studies [24,34] and one study [23] reported higher NBF and BIC around implants coated with ZOL, respectively. Jakobsen et al. [24] reported no significant difference in terms of BIC around implants coated with hydroxyapatite, PDLLA and ZOL compared with hydroxyapatite coated implants.

### Studies in sheep

*Topical delivery of ZOL*. One study [29] reported increased BA around implants placed in cavities irrigated with ZOL compared with controls (irrigation with saline).

## Quality assessment

The most common limitations were the short term and the incomplete follow up (up to 24 weeks) of the experimental groups. Furthermore, as all studies [17–36] were conducted in animal models, confounder's influence and the application of these results to human population is still limited and remains debatable. Thus, on average, the quality of included animal studies on the impact of topical ZOL administration on the osseointegration of implants was good, limitations of short-term follow up, lack of confounder's assessment and the need of clinical studies limit the application of these study outcomes. Quality assessment of the individual papers is summarized in Table 4.

### Studies in rats

The total quality score among the included studies ranged from 25 to 32, out of a maximum of 36 points. Ten categories were scored as excellent with coefficients between 0.8 and 1: item 1: title; item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5: methods/ethical statement; item 6: study design; item 7: experimental procedure; item 12: experimental outcomes; item 13: statistical analysis and item 16: outcome and estimation. Eight categories were scored as average with coefficients between 0.5 and 0.8: item 8: experimental animals; item 11: allocation; item 14: results/baseline data; item 15: number analysed; item 17: adverse events; item 18: discussion/

**Table 4.** Quality assessment according to ARRIVE guidelines of the included studies.

| Items | Studies in rats | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | T |
| Abtahi et al. [17] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 29 |
| Andersson et al. [18] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 0 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 2 | 32 |
| Back et al. [20] | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 26 |
| Gao et al. [31] | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 31 |
| Gao et al. [32] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 27 |
| Greiner et al. [33] | 1 | 2 | 2 | 0 | 2 | 1 | 1 | 2 | 0 | 0 | 0 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 25 |
| Peter et al. [26] | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 26 |
| Peter et al. [25] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 27 |
| Pyo et al. [27] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 2 | 1 | 2 | 29 |
| Stadlinger et al. [35] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 0 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 29 |
| Suratwala et al. [30] | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 0 | 2 | 0 | 2 | 1 | 0 | 1 | 2 | 1 | 2 | 1 | 1 | 26 |
| Ying et al. [38] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 0 | 1 | 2 | 0 | 2 | 1 | 2 | 28 |
| Category score (quality obtained) | 12 | 23 | 23 | 11 | 24 | 20 | 23 | 14 | 10 | 10 | 8 | 24 | 23 | 6 | 15 | 24 | 16 | 19 | 12 | 18 | |
| Maximum score by category (quality expected) | 12 | 24 | 24 | 12 | 24 | 24 | 24 | 24 | 24 | 24 | 12 | 24 | 24 | 12 | 24 | 24 | 24 | 24 | 24 | 24 | |
| Quality coefficients | 1 | .95 | .95 | .91 | 1 | .83 | .95 | .58 | .41 | .41 | .66 | 1 | .95 | .50 | .62 | 1 | .66 | .79 | .50 | .75 | |
| | Studies in rabbits | | | | | | | | | | | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | T |
| Arnoldi et al. [19] | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 2 | 32 |
| Dundar et al. [37] | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 0 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 29 |
| Qi et al. [28] | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 0 | 2 | 2 | 0 | 1 | 2 | 0 | 1 | 1 | 1 | 25 |
| Roshan-Ghias et al. [36] | 0 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 28 |
| Category score (quality obtained) | 3 | 7 | 8 | 4 | 8 | 6 | 8 | 4 | 8 | 4 | 2 | 8 | 8 | 3 | 5 | 7 | 5 | 6 | 4 | 6 | |
| Maximum score by category (quality expected) | 4 | 8 | 8 | 4 | 8 | 8 | 8 | 8 | 8 | 8 | 4 | 8 | 8 | 4 | 8 | 8 | 8 | 8 | 8 | 8 | |
| Quality coefficients | .75 | .87 | 1 | 1 | 1 | .75 | 1 | .50 | 1 | .50 | .50 | 1 | 1 | .75 | .62 | .87 | .62 | .75 | .50 | .75 | |
| | Studies in dogs | | | | | | | | | | | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | T |
| Baas et al. [39] | 0 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 0 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 29 |
| Cuairan et al. [21] | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 0 | 1 | 0 | 2 | 2 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 28 |
| Jakobsen et al. [22] | 1 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 0 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 28 |
| Jakobsen et al. [23] | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 0 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 30 |
| Jakobsen et al. [24] | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 0 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 30 |
| Tanzer et al. [34] | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 0 | 0 | 1 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 25 |
| Category score (quality obtained) | 5 | 12 | 12 | 6 | 10 | 9 | 12 | 7 | 0 | 7 | 5 | 12 | 11 | 5 | 12 | 12 | 12 | 8 | 6 | 7 | |
| Maximum score by category (quality expected) | 6 | 12 | 12 | 6 | 12 | 12 | 12 | 12 | 12 | 12 | 6 | 12 | 12 | 6 | 12 | 12 | 12 | 12 | 12 | 12 | |
| Quality coefficients | .83 | 1 | 1 | 1 | .83 | .75 | 1 | .58 | 0 | .58 | .83 | 1 | .91 | .83 | 1 | 1 | 1 | .66 | .50 | .58 | |
| | Studies in sheep | | | | | | | | | | | | | | | | | | | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | T |
| Stadelmann et al. [29] | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 1 | 1 | 24 |
| Category score (quality obtained) | 1 | 2 | 2 | 1 | 2 | 0 | 2 | 1 | 0 | 0 | 0 | 2 | 2 | 0 | 2 | 2 | 1 | 2 | 1 | 1 | |
| Maximum score by category (quality expected) | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | |
| Quality coefficients | 1 | 1 | 1 | 1 | 1 | 0 | 1 | .50 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | .50 | 1 | .50 | .50 | |

Item 1: title; item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5: methods/ethical statement; item 6: study design; item 7: experimental procedure; item 8: experimental animals; item 9: housing and husbandry; item 10: sample size; item 11: allocation; item 12: experimental outcomes; item 13: statistical analysis; item 14: results/baseline data; item 15: number analysed; item 16: outcome and estimation; item 17: adverse events; item 18: discussion/interpretation and scientific implications; item 19: general applicability and relevance; item 20: funding and conflict of interest. T: total score obtained by each manuscript (maximum 36 points).

interpretation and scientific implications; item 19: general applicability and relevance; and item 20: funding and conflict of interest. Lastly, two categories were scored as being of poor quality with coefficients <0.5: item 9: housing and husbandry; and item 10: sample size.

### *Studies in rabbits*

The total quality score among the included studies ranged from 25 to 32, out of a maximum of 36 points. Eight categories were scored as excellent with coefficients between 0.8 and 1: item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5: methods/ethical statement; item 7: experimental procedure; item 9: housing and husbandry; item 12: experimental outcomes; and item 13; statistical analysis. Twelve categories were scored as average with coefficients between 0.5 and 0.8: item 1: title; item 6: study design; item 8: experimental animals; item 10: sample size; item 11: allocation; item 14: results/baseline data; item 15: number analysed; item 16: outcome and estimation; item 17: adverse events; item 18: discussion/interpretation and scientific implications; item 19: general applicability and relevance; and item 20: funding and conflict of interest. None of the categories were scored as being of poor quality (coefficients <0.5).

### *Studies in dogs*

The total quality score among the included studies ranged from 25 to 30, out of a maximum of 36 points. Thirteen categories were scored as excellent with coefficients between 0.8 and 1: item 1: title; item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5: methods/ethical statement; item 7: experimental procedure; item 11: allocation; item 12: experimental outcomes; item 13; statistical analysis; item 14: results/baseline data; item 15: number analysed and item 16: outcome and estimation; and item 17: adverse events. Six categories were scored as average with coefficients between 0.5 and 0.8: item 6: study design; item 8: experimental animals; item 10: sample size; item 18: discussion/interpretation and scientific implications; item 19: general applicability and relevance; and item 20: funding and conflict of interest. Lastly, one category was scored as being of poor quality with coefficients <0.5: item 9: housing and husbandry.

### *Studies in sheep*

The total quality score from the included study was 24 out of a maximum of 36 points. Eleven categories were scored as excellent with coefficients between 0.8 and 1: item 1: title; item 2: abstract; item 3: introduction/background; item 4: introduction/objectives; item 5: methods/ethical statement; item 7: experimental procedure; item 12: experimental outcomes; item 13; statistical analysis; item 15: number analysed; item 16: outcome and estimation; and item 18: discussion/interpretation and scientific implications. Four categories were scored as average with coefficients between 0.5 and 0.8: item 8: experimental animals; item 17: adverse events; item 19: general applicability and relevance; and item 20: funding and conflict of interest. Lastly, five categories were scored as being of poor quality with coefficients <0.5: item 6: study design; item 9: housing and husbandry; item 10: sample size; item 11: allocation; and item 14: results/baseline data.

## Discussion

Results from ~87% studies [17,18,21,23–39] in the experimental studies included in this systematic review showed that local delivery of ZOL (coating or topical) is effective in enhancing osseointegration and/or NBF around implants. These results seem persuasive enough to conclude that local administration of ZOL promotes osseointegration in animals. However, it seems difficult to replicate these experimental results in a clinical setting due to a number of reasons. First, it seems challenging to establish a reliable and accurate methodology to deliver ZOL locally around implant surfaces, that could offer the most predictable outcome (improve NBF and/or BIC). For example, in the study by Cuairan et al. [21] ZOL solution was injected for 60 seconds into the bone cavity prior the implants placement; whereas, in other studies ZOL was embedded into implants surfaces coated with cross-linked fibrinogen [17–19,36], PDLLA [20,23,33], CaP [27] and/or hydroxyapatite [25,26,28–32,34]. Moreover, the dose formulation and time of ZOL incorporation into implants surfaces as coatings varied widely among the included studies [17–20,23–36]; Stadelmann et al. [29] soaked Ti implants coated with hydroxyapatite for 48 hours in 5 ml ultrapure water solution with $2.25 \times 10^{-5}$mol $L^{-1}$ of ZOL; whereas Suratwala et al. [30] soaked hydroxyapatite-coated nails in a 50 M of ZOL solution for five minutes. This suggests a lack of standardization regarding the methods and formulations to deliver ZOL locally, and the need to be further optimized. Such parameters should be taken in consideration in a future protocol for the clinical use of BPs in implantology. Second, it is well known that implant surface characteristics play an essential role in osseointegration promotion around implants references. From the literature reviewed, it is noteworthy that 74% of the studies [18,19,22–32,34,35,37,39] used rough surfaced implants. Studies [47–49] have shown higher proliferation of osteoprogenitor cells around rough surfaced implants compared to implants with turned surfaces. Furthermore, hydroxyapatite and CaP (which were used as carriers to immobilize ZOL into the implants surfaces) enhance osteoconductivity, biocompatibility and promotes higher peri-implant bone formation, bone mineralization and stability [50–52]. Therefore, it is hypothesized that in addition to ZOL, implant surface roughness and/or the surface modification may also contribute to attract osteoblast toward implant surfaces enhancing bone apposition.

It is pertinent to mention that the animal studies [17–39] included in the present review were performed for a maximum follow-up period of 24-weeks. It remains unclear whether local delivery of ZOL in humans receiving dental implants would increase BIC and contribute to long-term success and survival of dental implants. Furthermore, the role of

confounding parameters (such as poorly controlled diabetes mellitus, deficient oral hygiene and tobacco habits) as risk factors for healing impairment and enhanced alveolar bone loss are well established [53–56]. Since all studies [17–39] included in this systematic review were performed in animals, it remains to be determined whether or not ZOL local administration in a clinical scenario would facilitate NBF in patients with a poor plaque control, elderly individuals, systemically compromised and habitual tobacco product users. Furthermore, animal models usually report more profound effects of any given therapy. Thus, it is relevant to consider, whether or not the differences observed translate into humans in a clinically significant way. Moreover, in a recent *in vitro* study by Kos et al. [57] increased bacterial colonization (*Streptococcus mutans*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*) and biofilm formation was detected in hydroxyapatite discs coated with ZOL compared with uncoated controls. Additionally, ZOL and other BPs are considered a major risk factor to develop medication-related osteonecrosis of the jaw among patients undergoing dentoalveolar surgery [9,58,59]. Regardless of the fact that apparently low doses of ZOL are needed to promote NBF, the potential risks associated with local ZOL therapy cannot be disregarded. Therefore, these risk factors should be taken into consideration in a future protocol for the use of local ZOL in implantology in humans.

## Conclusions

Local ZOL delivery (coating or topical) seems to enhance osseointegration in animals; however, from a clinical perspective, further randomized control trials with long-term follow-up are needed in this regard.

## Disclosure statement

The authors declare that they have no conflicts of interest.

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