Efficacy of systemic bisphosphonate delivery on osseointegration of implants under osteoporotic conditions: Lessons from animal studies

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Abstract

Background: The aim was to systematically review the role of systemic bisphosphonate (BP) delivery on osseointegration of implants under osteoporotic conditions.

Methods: The addressed focused question was “Does systemic BP delivery enhance osseointegration of implants under osteoporotic conditions?” PubMed/MEDLINE and Google-Scholar databases were searched from 1994 up to and including December 2013 using different combinations of the following keywords: “bone to implant contact”, “implant”, “bisphosphonate”, “osseointegration” and “osteoporosis”. Review articles, case-reports, commentaries, letters to the Editor, unpublished articles and articles published in languages other than English were excluded.

Results: Fifteen animal studies fulfilled our eligibility criteria. Osteoporotic conditions were induced via bilateral ovariectomy (OVX). BPs used in the studies were ibandronate, zoledronic acid and alendronate. Results from 12 studies showed that systemic BP delivery significantly increased bone volume and bone-to-implant contact under osteoporotic conditions. Two studies reported no significant difference in osseointegration among OVX animals with and without systemic BP delivery. In one study, systemic BP delivery negatively influenced implant osseointegration. Rough-surfaced and polished implants were used in 11 and one study respectively. In 3 studies implant surface characteristics remained unclear.

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Conclusion: Within the limits of the present study, it is concluded that systemic BP delivery enhances implant osseointegration in animals with induced osteoporotic conditions. However, in a clinical scenario, the potential risk of BP related ONJ in osteoporotic patients undergoing dental implant therapy cannot be disregarded.

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1. Introduction

Osteoporosis, a metabolic disease of bone, is characterized by reduced bone mineral density (BMD) and bone mass due to impaired bone metabolism.1,2 In addition, osteoblasts in osteoporotic bone demonstrate impaired proliferative, synthetic and reactive ability to cellular mediators.1,3,4 Risk factors of osteoporosis include pre- and postmenopausal oestrogen deficiency, excessive glucocorticoid intake, eating disorders and gene interactions in bone metabolism.5–8

Bisphosphonate (BP) therapy is the treatment choice for the management of osteoporosis.9,10 These drugs act by inhibiting osteoclastic differentiation and maturation thereby leading to their dysfunction. Moreover, bisphosphonates induce osteoclastic apoptosis and reduce bone resorption by down-regulating bone turnover.11 This translates to improved BMD and structural bone properties and, reduced bone remodelling and risk of fractures in osteoporosis.12–14

Dental implants are modern substitutes for fixed and removable dental prosthesis that can osseointegrate and remain functionally stable over long durations.15,16 However, immunocompromised patients (such as those with poorly controlled diabetes, acquired immune deficiency syndrome and osteoporosis) are more susceptible to implant failure as compared to systemically healthy individuals.17–19

This may possibly be associated with impairment in bone healing following implant placement in such patients.18 Furthermore, a reduced BMD decreases bone to implant contact (BIC) and implant-bone shear strength; thereby increasing the risk of implant failure.17,20,21

Since BP therapy improve BMD in osteoporotic patients,22 it is tempting to speculate that BIC and bone volume (BV) are significantly higher around implants placed in osteoporotic patients under systemic BP therapy compared to osteoporotic patients not receiving systemic bisphosphonates. Therefore, the aim of the present study was to systematically review currently available evidence regarding the efficacy of systemic BP delivery on osseointegration of implants under osteoporotic conditions.

2. Materials and methods

2.1. Focused question

The addressed focused question was “Does systemic BP delivery enhance osseointegration of implants under osteoporotic conditions?”

2.2. Eligibility criteria

The following eligibility criteria were entailed: (a) original studies; (b) clinical and experimental studies; (c) intervention: role of systemic BP delivery in enhancing osseointegration under osteoporotic conditions; (d) use of a control group (ovariectomized [OVX]) animals receiving either placebo or no systemic drug delivery; (e) articles published only in English language. Review articles, case-reports, commentaries, letters to the Editor and unpublished articles were excluded.

2.3. Search strategy

PubMed/Medline (National Library of Medicine, Bethesda, MD) and Google-Scholar databases were searched from 1994 up to and including December 2013 using different combinations of the following keywords: “implant”, “bisphosphonates”, “osseointegration”, “osteoporosis” and “bone to implant contact”. Titles and abstracts of studies that fulfilled the eligibility criteria were screened by the authors and
checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently assessed against the eligibility criteria. Following this, reference lists of original and review studies that were found to be pertinent in the previous step were hand-searched and checked for agreement via discussion among the authors (Fig. 1).

The initial search yielded 23 studies. Eight studies, which did not fulfil the eligibility criteria, were excluded (Appendix A). In total, 15 studies were included and processed for data extraction.

3. Results

3.1. General characteristics of the studies

The general characteristics of the included studies are summarized in Table 1. All studies were experimental and were performed at university settings. Thirteen studies were performed in rats (aged between 1 and 12 months) and 2 studies were performed in rabbits (aged between 6 and 12 months). In all studies osteoporotic conditions were induced through bilateral ovariectomy under general anaesthesia. BP intervention included the use of ibandronate (IBN), zoledronic acid (ZOL) and alendronate (ALO) in one, four, and ten studies respectively. In 11 studies, subcutaneous BP administration was performed and oral and intravenous (IV) bisphosphonates were administered in two and two studies respectively. The doses for IBN, ZOL, and ALO were 1 × 10^{-3} to 25 × 10^{-3} mg/kg, 0.1 mg/kg and 5 × 10^{-2} to 10 mg/kg, respectively. Four studies compared the effect of ALO to estradiol on osseointegration under osteoporotic conditions; however Skripitz et al. compared the effects of ALO with parathyroid hormone (PTH) and ALO with calcitonin, respectively. The follow-up period after implant placement ranged between 3 days and 12 weeks. Implants were placed in tibia and femur bones in ten and three studies, respectively. In studies by Mardas et al., Cardemil et al. and Viera-Negron et al., implants were placed in the parietal bone, mandible and maxilla, respectively.

3.2. Implant shape and surface-related characteristics of the studies

The implant shape and surface-related characteristics of the studies that fulfilled our eligibility criteria are summarized in Table 2. In these studies, the numbers of implants placed ranged between 32 and 224. In nine studies, screw-shaped implants were used and cylindrical-shaped and rod-shaped implants were used in three and two studies, respectively. The diameters and lengths of implants used ranged between 1.5 and 5.0 mm and 3.0 and 12.0 mm, respectively. In 14 studies, titanium implants were used whereas Skripitz et al. placed bone cement rods in rat tibia. Rough-surfaced implants were used in 11 studies and one study used machined surface implants. In the studies by Cardemil et al., Viera-Negron and Duarte et al., implant surface characteristics remained unclear. In one, four and six studies ZOL, bone cement, sandblasted-acid-etched (SLA) and hydroxyapatite (HA) respectively were used as implant surface coatings. In the study by Qi et al., HA and ZOL coated implants were used. Mardas et al. compared the influence of SLA and modified SLA surface coatings on implant osseointegration under osteoporotic conditions.

3.3. Main outcome of studies

In all studies, histomorphometric and radiographic analyses and/or microcomputotomography of region of interest (i.e., bone-implant interface at the test and control sites) were performed. Results from 12 studies reported that systemic BP delivery significantly increased BV...
<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects (mean age)</th>
<th>Study groups</th>
<th>Implants placed in</th>
<th>Drugs used (dosage)</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Li et al.²³ (2013) | 46 rats (8 months)  | Group-1: 12 OVX  
Group-2: 12 OVX + ZOL  
Group-3: 12 sham operated | Tibia (iliac bone grafts)  
Tibia | ZOL 0.1 mg/kg (3 times) | 2 and 8 weeks | Compared to group 1, group 2 showed significantly increased BV/TV, IBCR and implant removal torque. Group 2 showed higher implant osseointegration at 14 days in tibia compared to OVX group. But less bone formation in mandible at 14 and 28 days. |
| Cardemil et al.²⁴ (2013) | 64 rats (3 months) | Group-1: 28 OVX  
Group-2: 28 OVX + ZOL | Tibia and mandible | Single IV ZOL 0.1 mg/kg (4 weeks before implantation) | 3, 14 and 28 days | Group 3 showed higher BV/TV, ICR and Conn.D than group 1. Group 4 should the highest values for higher BV/TV, ICR and Conn.D than other groups. |
| Qi et al.²⁵ (2012) | 56 rats (NA)       | Group-1: 8 OVX  
Group-2: 8 OVX + Loc-ZOL  
Group-3: 8 sham operated (control) | Tibia (iliac bone grafts)  
Groups 3 and 4: ZOL 0.1 mg/kg (4 times) | 12 weeks | Group 3 showed higher BV/TV, ICR and Conn.D than group 1. Group 4 should the highest values for higher BV/TV, ICR and Conn.D than other groups. |
| Chen et al.²⁶ (2011) | 40 rats (5 months) | Group-A: 10 sham operated  
Group-B: 10 OVX  
Group-C: 10 OVX + CT  
Group D: 10 OVX + ALO | Tibia | Group C: CT 5 IU/kg/day (90 doses)  
Group D: Oral ALO 7 mg/kg (12 times) | 12-weeks | Group D showed more volume of bone mass and osseointegration compared to groups B and C in osteoporotic rats. |
| Giro et al.²⁷ (2011) | 66 rats (1 month)  | Group 1: 10 control  
Group 2: 14 sham operated  
Group 3: 14 OVX  
Group 4: 14 OVX + estradiol (EST) (2 x 10⁻² mg/kg) (90 times)  
Group 5: 14 OVX + ALO (5 x 10⁻² mg/kg) (42 times) | Tibia | Group 4: Daily, 17b-estradiol (EST) (2 x 10⁻² mg/kg) (90 times)  
Group 5: Alternate day, ALO (5 x 10⁻² mg/kg) (42 times) | 12 weeks | Groups 4 and 5 showed significantly better BIC and BAFO than group 3. There was no difference in BIC and BAFO when comparing groups 4 and 5 to groups 1 and 2. |
| Mardas et al.²⁸ (2011) | 36 rabbits (6 months) | Group-1: 12 sham operated (controls)  
Group-2: 12 OVX  
Group-3: 12 OVX + ALO | Parietal bones (control)  
Groups 3 and 4: ZOL 0.1 mg/kg (4 times) | 4 and 16 weeks | At 4 weeks, BIC was lower in group 3 compared to other groups. ALO administration appeared to delay osseointegration of newly formed bone. |
| Yildiz et al.²⁹ (2010) | 36 rabbits (6–12 months) | Group 1: 12 sham operated (control)  
Group 2: 12 OVX  
Group 3: 12 OVX + ALO | Tibia | Group 3: Single dose IV ZOL 0.1 mg/kg (just before implant placement) | 8 weeks | BIC and bone generation was higher in group 3 compared to group 2. |
| Skripitz et al.³⁰ (2009) | 48 rats (4 months) | Group 1: 12 sham operated rats  
Group 2: 12 OVX  
Group 3: 12 OVX + PTH | Tibia | Group 3: Daily, PTH (6 x 10⁻² mg/kg), (14 times)  
Group 4: Daily, ALO (2 x 10⁻² mg/kg) (14 times) | 2 weeks | BIC and bone volume were higher for group 4 in comparison to group 2. |
| Giro et al.³¹ (2008) | 66 rats (2 months) | Group 1: 10 control  
Group 2: 14 sham operated  
Group 3: 14 OVX  
Group 4: 14 OVX + estradiol (EST) (2 x 10⁻² mg/kg) (90 times)  
Group 5: 14 OVX + ALO (5 x 10⁻² mg/kg) (42 times) | Tibia | Group 4: Daily, 17b-estradiol (EST) (2 x 10⁻² mg/kg) (90 times)  
Group 5: Alternate day, ALO (5 x 10⁻² mg/kg) (42 times) | 12 weeks | Cortical bone areas showed similar RBD for groups 4 and 5 which was higher than group 3. For cancellous areas RBD was greater in group 5 than all other groups. In osteoporotic conditions, BIC and bone density reduced in all groups. RBD and BIC was higher in group 4 as compared to group 3. |
| Viera-Negron et al.³² (2008) | 32 rats (6–9 months) | Group 1: 8 control  
Group 2: 8 ALO  
Group 3: 8 OVX  
Group 4: 8 OVX + ALO | Maxillary arch | Groups 2 and 4 were treated with ALO 5 mg/kg (24 times) | 4 weeks | Group 3 showed higher BV/TV, ICR and Conn.D than group 1. Group 4 should the highest values for higher BV/TV, ICR and Conn.D than other groups. |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Subjects (mean age)</th>
<th>Study groups</th>
<th>Implants placed in</th>
<th>Drugs used(^a) (dosage)</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Nakamura et al.\(^{33}\) (2008) | 64 rats (11 weeks)  | Group 1: 8 sham operated  
Group 2: 8 OVX  
Group 3: 8 OVX + ALO (12 weeks)  
Group 4: 8 OVX + calcitriol (12 weeks)  
Group 5: 8 OVX + ALO + calcitriol (12 weeks)  
Group 6: 8 OVX + ALO (4 weeks)  
Group 7: 8 OVX + calcitriol (4 weeks)  
Group 8: 8 OVX + ALO + calcitriol (4 weeks) | Femur               | Groups 3 and 5: Daily, ALO 0.1 mg/kg (84 times)  
Groups 4 and 5: Daily, calcitriol 1 × 10\(^{-4}\) mg/kg (84 times)  
Groups 6 and 8: Daily, ALO 0.1 mg/kg (28 times)  
Groups 7 and 8: Daily, calcitriol 1 × 10\(^{-4}\) mg/kg (28 times) | 4 weeks | Total bone mineral density was higher in all ALO groups compared to OVX group. Bone implant shear strength was greater in HA coated implants as compared to uncoated implants. |
| Giro et al\(^{34}\) (2007)  | 58 rats (2 months)  | Group 1: 10 control  
Group 2: 12 sham operated  
Group 3: 12 OVX  
Group 4: 12 OVX + estradiol (EST) (2 × 10\(^{-7}\) mg/kg) (90 times)  
Group 5: Alternate day, ALO (5 × 10\(^{-2}\) mg/kg) (42 times) | Tibia               | Group 4: Daily, 17b-estradiol (EST) (2 × 10\(^{-7}\) mg/kg) (90 times)  
Group 5: Alternate day, ALO (5 × 10\(^{-2}\) mg/kg) (42 times) | 12 weeks | Group 5 showed higher BMD and implant removal torque than other groups. |
| Duarte et al.\(^{35}\) (2005) | 87 rats (3 months)  | Group 1: 15 sham operated  
Group 2: 15 OVX  
Group 3: 15 OVX + ALO (80 days)  
Group 4: 14 OVX + ALO (40 days)  
Group 5: 14 OVX + estradiol (80 days)  
Group 6: 14 OVX + estradiol (40 days) | Tibia               | Group 3: ALO 5 mg/kg 4 days/week (45–46 times)  
Group 4: ALO 5 mg/kg 4 days/week (23 times)  
Group 5: 17b-estradiol 2 × 10\(^{-2}\) mg/kg daily (45–46 times)  
Group 6: 17b-estradiol 2 × 10\(^{-2}\) mg/kg daily (23 times) | 8 weeks | BIC in cancellous zone, BA and BMD were significantly greater for groups 3 and 4 as compared to group 2. |
| Kurth et al.\(^{36}\) (2005) | 84 rats (8 months)  | Group 1: 19 sham operated (control)  
Group 2: 24 OVX  
Group 3: 20 OVX + IBN (1 × 10\(^{-3}\) mg/kg)  
Group 4: 21 OVX + IBN (25 × 10\(^{-3}\) mg/kg) | Femur               | Group 3: Daily, IBN (1 × 10\(^{-3}\) mg/kg) (27 times)  
Group 4: Daily IBN (25 × 10\(^{-3}\) mg/kg) (27 times) | 27 days | Groups 3 and 4 showed higher osseointegration percentage as compared to group 2 for HA coated Ti implants. |
| Narai and Nagahata\(^{37}\) (2003) | 40 rats (3 months)  | Group 1: 15 sham operated (control)  
Group 2: 15 OVX  
Group 3: 10 OVX + ALO | Femur               | Group 3: ALO 7 × 10\(^{-2}\) mg/kg twice/week (8 times) | 4 weeks | Implant removal torque was significantly higher in group 3 compared to group 2. BIC was similar in groups 2 and 3. |

\(^a\) Drugs were administered subcutaneously unless mentioned.  
\(^b\) 60 days after implant placement OVX was performed, 90 days after OVX rats were sacrificed.
Table 2 - Description of implants characteristics in the studies included.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of implants placed</th>
<th>Bisphosphonate used</th>
<th>Implant dimensions (D x L mm)</th>
<th>Implant shape</th>
<th>Implant surface characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al.23 (2013)</td>
<td>24 in sham operated rats 24 in OVX rats 24 in OVX + ZOL rats</td>
<td>ZOL</td>
<td>2.0 × 12</td>
<td>Screw</td>
<td>Rough surface (plasma sprayed + HA coated)</td>
</tr>
<tr>
<td>Cardemil et al.24 (2013)</td>
<td>112 in OVX rats 112 in OVX + ZOL rats</td>
<td>ZOL</td>
<td>1.5 × 3.0</td>
<td>Screw</td>
<td>Ti alloya</td>
</tr>
<tr>
<td>Qi et al.25 (2012)</td>
<td>16 in sham operated rats 32 in OVX rats 32 in OVX + ZOL rats</td>
<td>ZOL</td>
<td>2.0 × 12.0</td>
<td>Screw</td>
<td>Rough surface (HA + ZOL coated)</td>
</tr>
<tr>
<td>Chen et al.26 (2011)</td>
<td>20 in sham operated rats 20 in OVX rats 20 in OVX + CT rats 20 in OVX + ALO rats</td>
<td>ALO</td>
<td>3.0 × 3.0</td>
<td>Cylinder</td>
<td>Rough surface (HA coated)</td>
</tr>
<tr>
<td>Giro et al.27 (2011)</td>
<td>10 in control rats 14 in sham operated rats 14 in OVX rats 14 in OVX + EST rats 14 in OVX + ALO rats</td>
<td>ALO</td>
<td>2.2 × 4.0</td>
<td>Cylinder</td>
<td>Rough surface (SLA)</td>
</tr>
<tr>
<td>Mardas et al.28 (2011)</td>
<td>24 in sham operated rabbits 24 in OVX rabbits 24 in OVX + ALO rabbits</td>
<td>ALO</td>
<td>5.0 × 3.0</td>
<td>Dome</td>
<td>Rough surface (Mod SLA and SLA)</td>
</tr>
<tr>
<td>Yildiz et al.29 (2010)</td>
<td>24 in sham operated rabbits 24 in OVX rabbits 24 in OVX + ZOL rabbits</td>
<td>ZOL</td>
<td>4.0 × 6.0</td>
<td>Screw</td>
<td>Rough surface (resorbable blast media using HA)</td>
</tr>
<tr>
<td>Skripitz et al.30 (2009)</td>
<td>12 in sham operated rats 12 in OVX rats 12 in OVX + PTH rats 12 in OVX + ALO rats</td>
<td>ALO</td>
<td>2.0 × 5.0</td>
<td>Rods</td>
<td>Rough surface (Palacos R, bone cement rods)</td>
</tr>
<tr>
<td>Giro et al.31 (2008)</td>
<td>10 in control rats 14 in sham operated rats 14 in OVX rats 14 in OVX + estradiol rats 14 in OVX + ALO rats</td>
<td>ALO</td>
<td>2.2 × 4.0</td>
<td>Screw</td>
<td>Rough surface (SLA)</td>
</tr>
<tr>
<td>Viera-Negron et al.32 (2008)</td>
<td>8 in control rats 8 in healthy + ALO rats 8 in OVX rats 8 in OVX + ALO rats</td>
<td>ALO</td>
<td>1.0 × 3.0</td>
<td>Screw</td>
<td>Titanium micro-screwsaba</td>
</tr>
<tr>
<td>Nakamura et al.33 (2008)</td>
<td>16 in sham operated rats 32 in OVX + ALO rats 32 in OVX + calcitriol rats 32 in OVX + ALO + calcitriol rats</td>
<td>ALO</td>
<td>1.4 × 23</td>
<td>Rods</td>
<td>Rough surface (HA coated) and non-coated implants</td>
</tr>
<tr>
<td>Giro et al.34 (2007)</td>
<td>10 in healthy rats 12 in sham operated rats 12 in OVX rats 12 in OVX + estradiol rats 12 in OVX + ALO rats</td>
<td>ALO</td>
<td>2.2 × 4.0</td>
<td>Screw</td>
<td>Rough surface (SLA)</td>
</tr>
<tr>
<td>Duarte et al.35 (2005)</td>
<td>15 in sham operated rats 15 in OVX rats 15 in OVX + ALO rats 29 in OVX + estradiol rats 28 in OVX + ALO rats</td>
<td>ALO</td>
<td>2.2 × 4.0</td>
<td>Screw</td>
<td>Pure Ti implantac</td>
</tr>
<tr>
<td>Kruth et al.36 (2005)</td>
<td>38 in sham operated rats 48 in OVX rats 82 in OVX + IBN rats</td>
<td>IBN</td>
<td>1.0b</td>
<td>Cylinder</td>
<td>Uncoated Ti implants and rough surface (HA coated) implants</td>
</tr>
<tr>
<td>Narai and Nagahata37 (2003)</td>
<td>15 in sham operated rats 15 in OVX rats 10 in OVX + ALO rats</td>
<td>ALO</td>
<td>1.95 × 4.0</td>
<td>Screw</td>
<td>Machined Ti surface</td>
</tr>
</tbody>
</table>

Ti, titanium; HA, hydroxyapatite; OVX, ovariectomised; ZOL, zoledronic acid; ALO, alendronate; IBN, ibandronic acid monosodium salt monohydrate; CT, calcitonin; PTH, parathyroid hormone.

a Implant surface characteristics not mentioned.
b Implanted length not mentioned.
and BIC around implants under osteoporotic conditions. One study, showed less bone formation and osseointegration for implants in O VX rats receiving BP therapy compared to controls. In two studies, there was no significant difference in BV and BIC around implants in O VX animals with and without systemic BP delivery.

4. Discussion

The present literature review was based on the hypothesis that systemic BP delivery enhances osseointegration of implants under osteoporotic conditions compared to when implants are placed under osteoporotic conditions without systemic BP delivery. Eighty percent studies included in the present review supported the aforementioned hypothesis. The dosage, frequency and route of BP delivery varied between the included studies. For example, in the study by Yildiz et al., IV ZOL at a dosage of 0.1 mg/kg was delivered once throughout the study period; whereas Nakamura et al. and Chen et al. administered 0.1 mg/kg and 7 mg/kg of oral ALO 84 times respectively throughout the study period. Although these studies reported systemic BP delivery to enhance osseointegration, a precise dosage and frequency of the drug that would yield the most favourable clinical outcome remains unclear. Moreover, it has been reported that the anatomy and jaw location influence the overall healing and outcome of dental implant therapy. In addition there is relatively greater bone turnover in jaws which is an explanation for the greater deposition of BP in the gnathic bones thereby increasing the risk of BP related osteonecrosis of the jaw (ONJ) as compared to extra gnathic sites. Among the studies included in the present review only two were performed in gnathic bones. Therefore there is a need for caution when using the results of studies included in the present review in clinical situations. Since BP dosages varied between the studies and that most experiments were performed in extragnathic bones it is exiguous to clinically correlate the results of the present review.

Implant surface roughness is directly associated with the degree of primary stability achieved and long-term implant success rate. Increase in surface roughness also facilitates the attachment of osteoprogenitor cells to implant surfaces thereby enhancing the bone volume and BIC around implants. From the literature reviewed, rough-surfaced implants were used in nearly 73% studies. Mardas et al. despite using rough-surfaced implants reported negative outcomes of systemic BP delivery on osseointegration under osteoporotic conditions. This may possibly be associated with the study methodology since dome-shaped implants were placed on grooved parietal bone surfaces instead of using conventional trephine-drilled full thickness osteotomies.

From a clinical perspective, experimental studies which reported systemic BP therapy to enhance osseointegration may be challenged. Besides a direct association that exists between osteoporosis and oestrogen deficiency; osteoporosis has also been related to advancing age and chronic hyperglycaemia. It has been reported that advancing age and chronic hyperglycaemia lead to increased formation and accumulation of advanced glycation end products (AGEs) in oral and systemic tissues of affected patients than healthy and younger individuals. AGEs have been reported to jeopardize the function of osteoblast and osteoclasts and induce oxidative stress and inflammatory response in the tissues. It is also pertinent to mention that osteoporosis was the only systemic condition induced in all studies which was established between 3 and 28 weeks after bilateral OVX in animals aged up to 12 months. It is speculated that under clinical settings, the beneficial effects of systemic BP therapy on osseointegration are compromised in elderly osteoporotic patients with adjunct systemic conditions (such as chronic hyperglycaemia) than in relatively younger osteoporotic patients without other systemic diseases.

Although BP is an effective anti-resorptive drug for the management of osteoporosis, there are concerns about their long-term usage. In a case series on eight patients, Ing-Lorenzini et al. reported that 50% of the patients develop a stress fracture or complete fracture on long-term (up to eight years) use of ALO. Rosenthal et al. also reported that long-term BP therapy may enhance the formation of micro-cracks femoral surgery. Therefore, it is imperative for dental clinicians to be aware of the possible complications of implant therapy (such as ONJ and bone micro-fractures) in osteoporotic patients receiving BP for prolonged durations.

5. Conclusion

Within the limits of the present study, it is concluded that systemic BP delivery enhances implant osseointegration in animals with induced osteoporotic conditions. However, in a clinical scenario, the potential risk of BP related ONJ in osteoporotic patients undergoing dental implant therapy cannot be disregarded.

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Competing interests

None declared.

Ethical approval

Ethical committee at College of Dentistry, King Saud University, duly approved the study (FR-0120).

Authors’ contributions

Fahim Vohra and Mohammad Qasim Al-Rifaiy performed the literature search and wrote the manuscript. Khalid Almas formatted the tables. Fawad Javed formatted Fig. 1 and revised
the manuscript. Fahim Vohra, Mohammad Qasim Al-Rifaï, Khalid almas and Fawad Javed designed the study and reviewed the manuscript prior to submission.

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

Li YF, Li XD, Bao CY, Chen QM, Zhang H, Hu J. Promotion of peri-implant bone healing by systemically administered parathyroid hormone and zoledronic acid adsorbed onto the implant surface. Osteoporos Int. 2013 Mar;24(3):1063–71 (Focused question not answered)


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