Bisphosphonates’ use and risk of aseptic loosening following total hip arthroplasty: a systematic review

Vasileios F Pegios1,2, Eustathios Kenanidis1,2, Stavros Tsotsolis2,3, Michael Potoupnis1,2 and Eleftherios Tsiridis1,2

1Academic Orthopaedic Department, Aristotle University Medical School, General Hospital Papageorgiou, Thessaloniki, Greece
2Centre of Orthopaedic and Regenerative Medicine (CORE), Center for Interdisciplinary Research and Innovation (CIRI)-Aristotle University of Thessaloniki (AUTH), Balkan Center, Thessaloniki, Greece
3Department of Trauma and Orthopaedics, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

• Purpose: The main indication of bisphosphonates (BPs) is osteoporosis treatment. However, there is growing interest in peri- and postoperative use of BPs to mitigate total hip arthroplasty (THA) aseptic loosening (AL) risk. This systematic review aimed to evaluate the implant survival and the AL rate in patients with elective THA receiving BPs compared to those that do not receive BPs. Secondary outcomes included the comparison of revision rate, postoperative complications, and patients’ functional scores.
• Methods: This systematic review was conducted under the PRISMA 2020 guidelines with a pre-registered PROSPERO protocol. Three engines and grey literature were searched up until May 2022. Randomized and nonrandomized controlled trials and comparative cohort studies assessing BP and control therapy impact on THA survival were included.
• Results: Twelve studies embraced the inclusion criteria. A total of 99 678 patients and 99 696 THAs were included; 10 025 patients received BPs (BP group), and 89 129 made up the control group. The overall revision and AL rates were lower in the BP group (2.17% and 1.85%) than in the control group (4.06% and 3.2%). Periprosthetic fracture (PPF) cases were higher in the BP group (0.24%) than in the control group (0.04%); however, the majority of PPF cases were derived from a single study. Further complication risk was similar between groups. Most studies reported comparable functional scores between groups.
• Conclusion: BP treatment after elective THA seems to reduce the overall revision and AL risk. Other complications’ risk and functional scores were similar between groups. Further high-quality studies are needed to validate the results due to the multifactorial AL pathogenesis.

Introduction

Total hip arthroplasty (THA) has proved to be an effective surgical operation with a high success rate, patient satisfaction and overall survival rates (1). A recent meta-analysis demonstrated 85.7% and 77.6% THA survival at 15 and 25 years, respectively (2). The most common causes of THA failure are aseptic loosening (AL), deep periprosthetic joint infections (PJI) and instability, followed by periprosthetic fractures (PPF), dislocations, implant breakage and metallosis (3, 4). The proper implants’ osseointegration is vital for a long-lasting THA, depending on multiple peri- and post-operative factors (5). Hip dysplasia, rheumatoid arthritis, avascular necrosis, younger age and male sex have been linked with the increased failure rate (4, 5, 6). The type of implant fixation, the surgical approach and the surgeon’s technical expertise can also affect the THA outcomes (3, 4, 5).

AL is one of the most common causes of THA failure in the mid to long postoperative term. AL is the failure of a noninfected prosthesis due to the loss of implant fixation over time (7, 8). Insufficient primary fixation and particle-induced osteolysis around the implant have been implicated. Prosthesis micromotion, particulate debris formation and macrophage-activated osteolysis are critically involved in AL pathogenesis (9, 10). The risk of AL based on the type of THA bearing surface, design, implant type, coating and porosity has been extensively studied so far (8, 9, 10, 11). Several diseases, such as diabetes mellitus, rheumatoid arthritis, Parkinson’s disease, previous surgical procedures, perioperative drug use, and other comorbidities, have also been evaluated.
(11, 12, 13, 14, 15, 16, 17). On top of that, there is growing interest in the peri- and post-operative use of anti-resorptive therapies, such as bisphosphonates (BPs), to mitigate the risk of THA AL.

BPs are the most widely used drugs to treat osteoporosis (18). BPs inhibit osteoclast activity, thus impeding bone resorption, suppressing the bone remodeling process, and ultimately increasing bone mineral density (BMD), effectively reducing the fracture risk (19). The BPs’ impact on implant fixation in patients undergoing THA has also been evaluated. Numerous studies supported that BPs therapy minimizes periprosthetic bone loss, reduces implants’ axial rotation and offers better clinical THA outcomes (20, 21, 22, 23, 24, 25). However, these parameters do not necessarily ensure the longevity and survival of THA.

This systematic review aims to thoroughly and critically appraise the available literature evaluating the implant survival and the AL risk of patients receiving BPs after elective THA compared to patients who do not receive BPs. Secondary outcomes included the overall revision rate, the patients’ functional outcomes and the postoperative complications.

Materials and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (26). The review protocol was pre-registered in the International Prospective Register of Systematic Reviews PROSPERO under the registration number CRD42021288596.

Search strategy

A thorough search for relevant studies published from inception until May 2022 was held in PubMed, Cochrane Library and Scopus. In addition, the reference lists of all studies were perused, and grey literature in the form of ongoing clinical trial protocols (ClinicalTrials.gov) and conference abstracts submitted in respectable orthopedic journals was hand-searched. The detailed search strategy for all explored databases can be found in the Supplementary Data File 1 (see section on supplementary materials given at the end of this article).

Eligibility criteria

The following PICO components were used as inclusion criteria for this systematic review: (i) population: patients undergoing elective THA; (ii) intervention exposure: perioperative BP therapy; (iii) comparison group: THA patients not receiving BP therapy; (iv) outcome: THA AL and survival rate.

Specific inclusion criteria were the following: (i) randomized (RCTs) and nonrandomized controlled trials, prospective and retrospective cohort (RCS) and comparative studies; (ii) studies involving adult patients (>18 years) that underwent elective THA; (iii) studies evaluating the impact of at least one perioperative dose of BP treatment on the THA survival rate; (iv) studies providing extractable data; (v) studies investigating the effect of different BP therapies.

On the other hand, studies were excluded if they (i) reported the effect of BPs therapy on periprosthetic BMD, implant osseointegration or migration without evaluating the THA survival; (ii) were narrative reviews, case series and reports, letters to the editor or editorial comments; (iii) were conducted in animals or cadavers; (iv) were written in a non-English language; (v) had no full-text available.

Outcomes

The primary outcome of this systematic review was the effect of BPs therapy on the survival and AL rate of elective THAs. Secondary outcomes included the overall revision rate, the patients’ functional outcomes and the postoperative complications.

Study selection and data extraction

Two investigators (VFP and ST) individually screened all the eligible articles based on title and abstract. Subsequently, full texts of the selected records were evaluated based on the inclusion criteria. Duplicate reports were excluded. Discrepancies between the two authors were resolved via discussion with a senior author (EK).

These investigators (VFP and ST) reviewed the articles separately and extracted the data for each included study. Data were imported into a predefined Microsoft Excel spreadsheet. They incorporated information about the study design (title, first author, country of origin, publication date, journal, study type, time of recruitment, inclusion and exclusion criteria, outcomes, number of patients, BP use, concomitant therapy, treatment onset and duration, follow-up), baseline population characteristics (sex, age, body mass index, comorbidities, DEXA scores, surgical approach, type of fixation and implant characteristics, functional scores), and primary and secondary outcomes (drop-out rate, all-cause revision, AL, infectious loosening, periprosthetic or implant fracture, dislocation, osteolysis, functional scores). A pilot test before the data extraction was performed to establish reviewing compatibility between the two authors.

Continuous values were presented with mean and standard deviation (SD), while categorical values were presented as absolute or relative frequencies. Data
conversions were performed according to the formulas by Wan et al. (27).

Quality assessment

Two authors (VFP and ST) evaluated the quality of the included studies, and any discrepancies were resolved through discussion with a senior author (EK). We used The Cochrane Risk of Bias 2 tool (ROB 2) and the Newcastle-Ottawa Scale (NOS) to assess the methodological quality of RCTs and non-RCT cohort studies, respectively (28, 29). The ROB 2 is an outcome-based tool designed to evaluate the risk of bias in RCTs. It consists of several domains (randomization process, deviations from intended interventions, missing outcome data, outcome measurements, selection of the reported result, and overall bias). Each domain has ‘signalling questions’ that are utilized based on an algorithm to suggest an overall risk of bias judgement among ‘High’, ‘Some concerns’, or ‘Low’. The NOS is used for non-RCT cohort studies, and it consists of three domains, ‘Selection’, ‘Comparability’, and ‘Outcome’, with four, two and three variables in each domain, respectively. All variables can be scored with up to one star, except for ‘Comparability’, which can be scored with up to two stars. Afterwards, an overall study score is calculated, the maximum being nine stars. Studies are generally considered ‘Low quality’ with a score 0-3, ‘Moderate quality’ with a score 4-6 and ‘High quality’ with a score of 7-9.

Results

Search results

The initial literature search revealed 1597 results. After removing the duplicates and screening the titles and abstracts, 263 articles were considered relevant and evaluated as full texts. Finally, 12 studies met the eligibility criteria and were included in this systematic review. The reasons for all studies’ exclusion are provided in the Supplementary Data File 3. The screening and selection process is illustrated in Fig. 1.

Patient characteristics and studies’ design

The included studies were published between 2006 to 2019. Seven studies were RCTs (30, 31, 32, 33, 34, 35, 36) and five were RCSs (37, 38, 39, 40, 41). A total number of 99,678 participants undergoing 99,696 THAs were included. Forty-seven thousand two hundred eighty-nine patients were men. The mean age of patients at the time of THA was 65.14 ± 2.1, and the follow-up ranged from 2.6 to 15 years. Four studies reported long-term follow-up (≥10 years) (30, 37, 39, 40). Ninety-nine thousand one hundred fifty-four out of 99,678 patients were evaluated until the final follow-up period; 10,025 patients received BPs (BP group), and 89,129 made up the control group. Four studies evaluated zoledronic acid treatment (30, 32, 36, 40), two studies alendronate (34, 35), one risedronate (31) and one pamidronate treatment (33). Four studies assessed multiple BP treatments (37, 38, 39, 41). In the study of Yukizawa et al. the control patients were divided into two groups, one receiving alfacalcidol and the second receiving no intervention (35). Furthermore, Formica et al. evaluated the effect of multiple covariates, including BP administration on post-THA outcomes such as rate of neck resorption, AL, PFNs, infection and functional scores (40). The patients’ demographics and study characteristics are depicted in Table 1.

Operative and implant design data

Four studies reported the surgical approach (31, 32, 36, 40) and nine studies the type of fixation used (30, 31, 32, 33, 34, 35, 36, 40, 41). In detail, 78 were cemented, 10 441 cementless, 1879 hybrid, and 52 were reverse hybrid THAs. Eight studies shared information on the implant and bearing couple characteristics (30, 31, 32, 33, 34, 35, 36, 40). Detailed operative data are shown in Table 2.

Overall revision rate

Eleven studies reported the revision rate for any reason (30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41), whereas one studied only the AL rate, excluding all other revision causes (39); 218 individuals of the BP (2.17%) and 3617
Table 1  Demographics and study characteristics.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study type</th>
<th>Patients, n</th>
<th>BP group, n (%)</th>
<th>BP treatment</th>
<th>Control Group treatment</th>
<th>Sex</th>
<th>Age†</th>
<th>Time of THA</th>
<th>Follow-up (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aro et al. (30)</td>
<td>Finland</td>
<td>RCT</td>
<td>49</td>
<td>25 (51)</td>
<td>ZOL + Ca and vit D</td>
<td>Ca &amp; vit D</td>
<td>M</td>
<td>68.1 (9.1)</td>
<td>2008–2009</td>
<td>8–10†</td>
</tr>
<tr>
<td>Khatod et al. (41)</td>
<td>USA</td>
<td>RCS</td>
<td>12878</td>
<td>2292 (18)</td>
<td>N/A</td>
<td>N/A</td>
<td>F</td>
<td>66.7 (10.4)</td>
<td>2001–2010</td>
<td>8</td>
</tr>
<tr>
<td>Muren et al. (31)</td>
<td>Sweden</td>
<td>RCT</td>
<td>73</td>
<td>36 (49)</td>
<td>RIS + Ca &amp; vit D</td>
<td>Ca &amp; vit D</td>
<td>30</td>
<td>60.5 (7)</td>
<td>2006–2010</td>
<td>3.9–4.1†</td>
</tr>
<tr>
<td>Prieto-Alhambra et al. (37)</td>
<td>UK</td>
<td>RCS</td>
<td>23269</td>
<td>1052 (5)</td>
<td>AL, ET, IBAN, RIS ≤ Ca or Vit D or A/C ET, CLO, AL, TIL, RIS ≤ O/M</td>
<td>N/A</td>
<td>9564</td>
<td>69.98 (9.67)</td>
<td>1986-2006</td>
<td>15 (max)</td>
</tr>
<tr>
<td>Ro et al. (39)</td>
<td>South Korea</td>
<td>RCS</td>
<td>56043</td>
<td>5756 (10)</td>
<td>1 WHO-defined daily dose min 2 doses</td>
<td>N/A</td>
<td>1708</td>
<td>75.6 (8.9)</td>
<td>1998-2007</td>
<td>2.6b</td>
</tr>
<tr>
<td>Scott et al. (32)</td>
<td>USA</td>
<td>RCT</td>
<td>51</td>
<td>27 (53)</td>
<td>ZOL + Ca &amp; vit D</td>
<td>Ca &amp; vit D</td>
<td>23</td>
<td>61.2 (12.4)</td>
<td>2005–2008</td>
<td>2 (min)</td>
</tr>
<tr>
<td>Shetty et al. (33)</td>
<td>UK</td>
<td>RCT</td>
<td>47</td>
<td>23 (49)</td>
<td>PAM</td>
<td>Placebo</td>
<td>21</td>
<td>58.5 (12.4)</td>
<td>1998</td>
<td>5</td>
</tr>
<tr>
<td>Tapaninen et al. (34)</td>
<td>Finland</td>
<td>RCT</td>
<td>16</td>
<td>7 (44)</td>
<td>AL + Ca</td>
<td>Ca</td>
<td>7</td>
<td>61.4 (6.9)</td>
<td>1998-1999</td>
<td>0.5†</td>
</tr>
<tr>
<td>Yukizawa et al. (35)</td>
<td>Japan</td>
<td>RCT</td>
<td>60</td>
<td>20 (33)</td>
<td>AL</td>
<td>1st group: A/C, 2nd group: none Ca and vit D</td>
<td>14</td>
<td>65 (10)</td>
<td>2006–2007</td>
<td>9 (min)</td>
</tr>
<tr>
<td>Friedl et al. (36)</td>
<td>Austria</td>
<td>RCT</td>
<td>50</td>
<td>25 (50)</td>
<td>ZOL + Ca &amp; vit D</td>
<td>22</td>
<td>60.9 (12.8)</td>
<td>2002–2005</td>
<td>2.8³</td>
<td></td>
</tr>
<tr>
<td>Formica et al. (40)</td>
<td>Italy</td>
<td>RCS</td>
<td>176</td>
<td>57 (24)</td>
<td>ZOL + Ca &amp; vit D</td>
<td>N/A</td>
<td>78</td>
<td>74.7 (9.8)</td>
<td>1997–2006</td>
<td>14.2³</td>
</tr>
</tbody>
</table>

*Results are given as a range. †Results are given as median. ‡Results are given as mean and s.d. in parentheses. †At any time during the study period for primary surgery or prior to surgery for revisions. A/C, alfacalcidol; AL, alendronate; BP, bisphosphonate; Ca, calcium; CLO, clodronate; ET, etidronate; IBAN, ibandronate; IQR, interquartile range; N/A, not answered; O/M, other medication; PAM, pamidronate; RCS, retrospective cohort study; RCT, randomized controlled trial; RIS, risedronate; TIL, tiludronate; vit D, vitamin D; ZOL, zoledronate.
of the control group (4.06%) were revised for any reason (Table 3). Four studies demonstrated that BP therapy significantly affected the all-cause revision rate (37, 38, 39, 41). Khadot et al. supported that BP treatment protected patients for all-cause revision (HR: 0.5 (95% CI: 0.33, 0.74)), especially for the patients above 65 years taking BPs (HR: 0.48 (95% CI: 0.31, 0.74)). This study showed that patients with osteopenia or with osteoporosis under BP medication had better THA survival rates than those not taking BP treatment (HR: 0.49 (95% CI: 0.29, 0.84) and HR: 0.22 (95% CI: 0.08, 0.62), respectively), whereas patients with normal BMD that received or not BPs did not differ significantly (41). Prieto-Alhambra et al. also demonstrated a better implant survival rate in the BP than the control group (HR: 0.47 (95% CI: 0.24, 0.94)) (37). Another study by Prieto-Alhambra et al. revealed a better all-cause revision rate for BP than the control group involving both THAs and total knee arthroplasties (TKAs) (38). Concerning THAs, the overall survival was significantly better for the BP than the control group (HR: 0.3 (95% CI: 0.18, 0.51)). The benefits of BP treatment were only prominent for the patients who started BP postoperatively (adjusted HR 0.31 (95% CI: 0.17, 0.58)), after 1 year of BP treatment (P = 0.02) in patients with good BP compliance with a medication possession ratio ≥ 0.8 (HR 0.38 (95% CI: 0.24, 0.62)). Furthermore, patients over 75 years benefited more from BP treatment (HR 0.21 (95% CI: 0.10, 0.44)). The estimated number of patients who needed to treat with BPs to avoid one revision surgery in the first 2 postoperative years was 42 (38). Ro et al. assessed only the AL rate and excluded all other revision causes showed a significantly lower AL rate for both THAs and TKAs in the BP group (39). The other eight studies did not correlate significantly with the BP treatment and revision rate for any reason (30, 31, 32, 33, 34, 35, 36, 40).

### AL rate

Ten studies reported on AL rate (30, 31, 32, 33, 34, 35, 36, 39, 40, 41); 185 patients in the BP group (1.85%) and 2857 (3.2%) in the control group were revised due to AL (Table 3). Two studies found significant differences in favor of the BP groups. Khadot et al. demonstrated that the AL rate was significantly lower in the BP than in the control group (HR: 0.53 (95% CI: 0.34, 0.81)), with patients over 65 years taking BPs having the lowest AL rate than the control group (HR: 0.47 (95% CI: 0.29, 0.76)). This study also supported that patients with osteopenia and osteoporosis demonstrated significantly lower AL rates when treated with BPs after THA (HR: 0.53 (95% CI: 0.29, 0.99) and HR: 0.33 (95% CI: 0.11, 0.99), respectively) (41). Ro et al. showed that BP therapy diminished the AL risk (HR: 0.693 (95% CI: 0.587, 0.818)),...
especially if treatment lasted more than one year (HR: 0.49 (95% CI: 0.247, 0.972)) (39). Formica et al. found no significant AL difference between the BP and control groups (P = 1) (40). The rest seven studies did not report any case of AL in either group (30, 31, 32, 33, 34, 35, 36).

### Functional scores

Six studies assessed comparative functional outcomes between groups (Table 3) (30, 31, 32, 33, 34, 36, 40). Most studies supported no significant difference in functional outcome scores between the BP and the control group. Friedl et al. only reported a higher Harris hip score (HHS) for the BP than the control group during all follow-ups until the third postoperative year. It is also noteworthy that the control group had significantly better baseline HHS than the BP group (36).

### Complications

Eight studies evaluated the incidence of PPFs between groups (30, 31, 32, 33, 34, 35, 40, 41); however, only three studies reported PPF cases (30, 40, 41). Twenty-four PPFs occurred in the BP (0.24%), 34 in the control group (0.04%) and one was unclarified (40). Khatod et al. demonstrated a significantly higher PPF risk for the BP group (HR: 1.92 (95% CI: 1.13, 3.27)). Moreover, patients under 65 with normal DEXA scans were more likely to suffer a PPF if treated with BP (HR: 32.69 (95% CI: 2.65, 403.7)) (41). Aro et al. reported only one PPF case in the control group (30). Formica et al. studied the effect of several parameters on THA survival and bone resorption and reported one PPF case without specifying if it belonged to the BP-treated group (40).

Formica et al. also described two cases of PJIs without explaining their treatment group (40). Hip dislocation happened in one patient in the BP (0.01%) and four in the control group (0.004%). Two patients in the control group had revision surgery for either dislocation or infection, and the other two were treated conservatively (31, 35, 36). The BP dislocation was treated conservatively (33). Formica et al. reported one other case of dislocation without clarifying their treatment group (40). Moreover, one patient in the control group had an implant fracture, and one had a ceramic head fracture (32, 40). Heterotopic ossification was only reported in two studies; Muren et al. showed no difference in heterotopic ossification between groups (31), and Formica et al. reported three cases that were treated surgically but had no information about their group (40). Osteolytic lesions were reported in two studies. Shetty et al. described four cases and no significant difference between groups (33). Formica et al. also described two cases of PJIs without specifying if it belonged to the BP-treated group (40).

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### Quality assessment

The methodological quality of studies varied significantly. One RCT study (31) was rated as having a ‘low’ risk of bias, two studies (30, 33) as ‘Some concerns,’ and the rest four studies (32, 34, 35, 36) had a ‘high’ risk of bias. Four non-RCT studies (37, 38, 39, 41) were considered of high,
and one (40) was of moderate quality. Bias assessment data are presented in the Supplementary Data File 2.

Discussion

This systematic review aimed to assess the overall revision rate and especially the AL rate in patients undergoing primary THA that followed or did not follow BP treatment. Overall, the risk for revision due to AL when combining all included studies was lower in the BP group (1.85%) than in the control group (3.2%). Similarly, the risk for all-cause revision was lower in the BP group (2.17%) than in the control group (4.06%). Most studies reported equal functional scores and no differences in the rate of postoperative complications such as PJI and dislocations; PPFs were more frequent in the BP group.

AL is considered the most common late THA complication. It is usually characterized by a slow but steadily progressing loosening of, in other respects, well-fixed acetabulum or femoral stem. The AL diagnosis is still challenging, as there is no objective, reliable and repeatable measure of prediction of implant failure. AL signs and symptoms, such as radiographic radiolucent lines and the reported pain, are usually nonspecific. Blood tests and bone scans are also used to rule out the existence of septic AL. Consequently, AL diagnosis is commonly delayed and verified during the revision of THA surgery.

The AL etiology and pathophysiology have not been elucidated yet. AL is considered a complex, multifactorial process which involves biological and mechanical mechanisms causing the failure of hip prostheses. Improper primary fixation, mechanical fixation loss gradually, or biological loss of implant fixation produced by particle-induced osteolysis are the leading theories of AL pathogenesis. The inadequate initial fixation usually results from improper implant positioning during the index surgery, which may lead to implant micromotion. This mechanism eventually creates abnormal gaps between the bone-implant interface impeding the natural osseointegration process. Microparticle wear debris derive mainly from artificial joint materials, most commonly from polyethylene wear (8, 9, 10, 39, 42, 43). These microparticles mediate a foreign body response, releasing several inflammatory cytokines and kinases, which upregulate phagocytes and macrophages (8, 9, 42, 43, 44, 45). The macrophage exposure to wear debris and inflammatory cells induce periimplant osteoclastic activation and bone resorption (8, 9, 42). The size of the wear debris molecules depends on several factors and can variably affect the inflammatory response; smaller molecules cause greater upregulation and osteolysis (46, 47). Mechanical reasons, such as loading, increase fluid pressure and further disseminate the debris particles in the joint, playing a principal role in AL pathogenesis. The improper implant osseointegration and the created gaps allow joint fluid to build up inside them, increasing the periprosthetic hydrostatic pressure. As a result, the free debris molecules are further dispersed and distributed around the implant, and the inflammatory response and bone resorption are augmented (48, 49, 50). Whether BP treatment may prevent or stop the AL process is a concern but remains unresolved.

Several factors may influence the risk of AL following THA. The THA-bearing surface markedly affects the AL risk, with ceramic-on-polyethylene being the most beneficial, followed by ceramic-on-ceramic, metal-on-polyethylene and finally by metal-on-metal bearing surfaces (51, 52, 53, 54, 55). Acetabular screws favor primary stability and ensure better cup osseointegration (56), and trabecular metal acetabular cups benefit long-term osseointegration (57). Moreover, the implant coating type, porous covering extent, and the surgeon’s expertise may also affect the AL risk (58, 59, 60, 61). Additionally, numerous diseases such as diabetes mellitus, rheumatoid arthritis, sickle cell or Parkinson’s disease (11, 13, 14, 62), previous surgical operations such as spinal fusion or hip arthroscopy (63), and various drugs such as statins, beta-blockers and opioids have been implicated to the AL development (15, 16, 64). The AL pathogenesis is multifactorial. Unfortunately, the studies included in our systematic review did not control the groups for all these parameters, raising concerns about the outcomes.

BPs are drugs with high bone antiresorptive activity due to their osteoclast-inhibiting properties (65, 66, 67). BPs are widely used treatments in several medical diseases, most notably osteoporosis. Lately, BPs therapy has also been evaluated in the AL prevention or treatment following THAs. It is supported that postoperative BP treatment mitigates osteoclast activity, allowing an improved implant–host bone osseointegration process and long-lasting implant fixation, thus reducing the AL risk (42). Other theories speculate that BP therapy reduces the inflammatory inductive activation of osteoclasts from wear debris molecules and micromotion, leading to osteoclast apoptosis and weakened periprosthetic osteolysis (68). Our study showed that fewer patients in the BP group revised for AL than the control group, highlighting the potential beneficial effect of BPs in the AL process.

Another crucial parameter is the type of BP treatment, as various drugs demonstrate different efficacy. A recent network meta-analysis showed that various BPs therapy significantly increased BMD in the calcar region. Zoledronate was the more efficient during the first 12 months, followed by alendronate and etidronate, which
also had long-lasting residual effects after 12 postoperative months (69). Another meta-analysis also supported the positive impact of zoledronate on the periprosthetic BMD preservation and HHS improvement in osteoporotic patients in the first postoperative year after THA (20). Shi et al. also demonstrated that BP therapy decreases periprosthetic bone resorption in short-, medium-, and long-term periods (68). Our systematic review data do not allow comparisons between drugs. All the studies that reported significantly different AL rates among groups assessed the effect of the BPs in general without studying a particular BP drug. Higher-level studies evaluating other BP drugs are certainly needed.

The onset and duration of BP treatment may also affect the AL risk. Shi et al. supported that treatment duration over six months is more beneficial than less treatment (68). One of the included studies, showed that BPs treatment lasting for more than one year reduced the revision risk more efficiently than a shorter therapy (39). Prieto-Alhambra et al. also supported that BPs therapy was more effective after one year of postoperative treatment in patients with good drug compliance. Additionally, the positive effect of BP was apparent only when the onset of treatment was after the primary THA (38). Interestingly, another study found that the risk of failure decreased as the BP treatment was prolonged but increased among the short-term users (70). The duration and onset of the included studies were diverse.

Furthermore, the studies depicting the positive impact of the BP treatment on AL rate had a follow-up period of 4–10 years, while the rest of the studies that did not report any difference between groups had diverse follow-up periods. As a result, the variable follow-up of the included studies, in conjunction with the ranging onset time and duration of BP treatment, did not allow for an analysis of the effect of treatment time on the AL outcome.

The potential impact of the implant fixation technique on the reported revision rate outcome of studies was also undetermined. In uncemented fixation, the acetabular cup and the femoral stem are press-fitted in the bone, and the osseointegration process is based on forming new bone around the implants. In cemented THA, the cement mantle between the host bone and the implants ensures better fixation in patients with poor bone quality (4, 71). Khatod et al. showed that the BP therapy using cemented implants did not affect the rate of all-cause revision, AL, and PPFs (41). The rest of the included studies either did not report the type of fixation or did not find any difference regarding AL and overall revision risk. BP medication may be more helpful in uncemented THAs, as BPs’ mechanisms of action are mainly involved in the evolving osseointegration process between the implant and host bone. More studies are thus needed to estimate the AL risk of BP treatment after THA comparing cemented and uncemented fixation.

One of our systematic review studies demonstrated that the BP group had an ignorantly higher PPF rate overall. Patients under 65 years with normal DEXA scans were at a significantly higher PPF risk if they were under BP medication (41). Although the PPF cases of our study had higher frequency in the BP than in the control group, the majority of PPFs came from this study (41). This oxymoron result opposes the main BP treatment effect, bone loss reduction. Possible explanations include that these PPFs were not osteoporotic but higher energy traumas or a short duration of postoperative BP treatment incapable of protecting the patients. BP medication and PPF risk after elective THA must be further elucidated.

Functional scores were reported in less than half of the included studies; only one study found a favorable impact of BP treatment on postoperative functional scores (36). As a result, this systematic review could not conclude the effect of BP treatment on postoperative functional scores. The antiresorptive effect of postoperative BP medication can reduce periprosthetic bone loss, improving postoperative pain, discomfort and postoperative patient function. It is feasible that postoperative BP medication after elective THA in older patients can result in better functional improvement and patient satisfaction scores; thus, future research is highly recommended.

Our systematic review has several limitations. The first limitation is the relatively low quality of evidence in the included studies. However, half of the studies are RCTs, but only one was considered a low-risk bias study. The rest of the studies are non-RCT cohort studies; nevertheless, most were considered moderate to high methodological quality. Furthermore, the studies did not consistently report several crucial variables that may affect the AL rate. The type of BP treatment was inconsistently reported among studies, especially in the RCSs, where multiple BP therapies were assessed simultaneously. Drug dosage, administration route, duration of treatment and additional supplement therapies varied among the studies. Moreover, reported inconsistencies were noted in the surgical data, such as implant characteristics and fixation techniques. It is also noteworthy that most of the included studies reported only short- to midterm follow-up data; however, AL is considered a slow-progressing, late THA complication. All these factors increase the heterogeneity of this systematic review and raise doubts about the validity of the results.

Conclusion

AL is the most common late complication after THA, yet its pathophysiology is not fully understood. Multiple factors are involved in AL pathogenesis, activating osteoclasts...
and causing periprosthetic bone resorption. BP therapy seems to mitigate the risk of postoperative AL after THA. This systematic review combined all included studies and supported that the overall revision risk due to AL was lower in the BP group than in the control group. However, the published data on this topic are still ambiguous, with several studies reporting the benefits of BP treatment but others not reducing the AL rate after THA. The low quality of most of the studies, the incomplete comprehension of AL’s mechanisms and risk factors, and the multifactorial pathogenesis require more high-quality trials with long periods of patient follow-up to be published.

Supplementary materials
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References
17. Kapadia BH, Issa K, Pivec R, Bonutti PM & Mont MA. Tobacco use may be associated with increased revision and complication rates following total hip arthroplasty. Journal of Arthroplasty 2014 29 777–780. (https://doi.org/10.1016/j.arth.2013.08.023)


