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Do bisphosphonates reduce early micromotion and periprosthetic bone loss in total knee arthroplasty? A review of the evidence

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Abstract Early micromotion of implant components and periprosthetic bone loss in patients undergoing total knee arthroplasty are thought to contribute to late aseptic loosening. In the pursuit of longer implant survival, the administration of bisphosphonates may be advocated as a means to buffer implants against microinstability and periprosthetic bone loss. A bibliographic search identified one meta-analysis and two randomised controlled trials dealing with this topic. Current evidence supports the hypothesis that the inhibiting effects of bisphosphonates on bone resorption reduce implant micromotion and periprosthetic bone loss at the one-year follow-up. Tested bisphosphonates include clodronate, pamidronate and alendronate. However, a decline in periprosthetic BMD is observed at the three-year follow-up following a six-month course of bisphosphonate administration. Length of follow-up in available studies is currently too short to determine whether bisphosphonates increase the longevity of implants. Furthermore, the optimal dose, modality and length of bisphosphonate administration have yet to be determined.

Key words Bisphosphonates • Total knee arthroplasty • Total knee replacement • Bone loss • Evidence

Introduction

The Swedish Knee Arthroplasty Register (SKAR) has indicated that implants used in total knee arthroplasty (TKA) perform differently when implant revision following aseptic loosening is used as an end-point [1]. Although the type of variables affecting the survivorship of implants used in TKA has not yet been clarified, the long-term survival of TKA prostheses potentially depends on a complex interaction of factors that are implant-, surgeon- and patient-related. Implant-related factors include structural properties such as the type of alloy, its design and surface finishing, and the tribologic properties of the ultra-high molecular weight polyethylene. Factors that are surgeon-dependent encompass a meticulous surgical technique, proper soft-tissue balancing, a correct alignment of the implant components and achieving adequate primary stability. Patient-related factors are represented by age and relevant level of activity, secondary stability relying on osteointegration and the immune response to debris generated by wear.

One poorly understood factor implicated in implant survival is the short-term biological response of host bone cells to the bone-implant or bone-cement interface. The coupling of bone with biomaterials of a higher elastic modulus can cause a stress-shielding effect, namely a reduced stress transfer to surrounding bone that thus undergoes a decrease in its bone mineral density (BMD). As far as TKA is concerned, it has been recognised that

fixation of the tibial component represents the weakest link due to the inferior trabecular bone volume at the tibial metaphysis level as opposed to that of the distal femur, among other factors [2]. However, periprosthetic bone loss does occur at the femoral component level as well [2]. The periprosthetic bone loss may be compounded by the age-related decrease in BMD, particularly in elderly women bearing the long-term aftermaths of postmenopausal osteoporosis.

On the basis of biomechanical analyses [2], it has been advocated that stress-shielding induced by an implant on the surrounding trabecular bone, both at the proximal tibial and distal femoral metaphysis levels, is capable of bringing about loosening of the components after cycling loading. The loss of BMD may undermine the capacity of trabecuar bone to resist stresses imparted by the implant, ultimately leading to bone fatigue failure. The theoretical assumptions of biomechanical analysis are supported by clinical studies suggesting that periprosthetic bone loss adversely affects the survival of implants [3, 4].

Since bisphosphonates have been shown to inhibit bone resorption in animals and humans [5], numerous studies have investigated whether this class of drugs reduces implant micromotion and periprosthetic bone loss following total joint replacement. Therefore, in the present paper, we review the evidence for the use of bisphosphonates in TKA and assess their potential use in routine clinical practice.

Materials and methods

A bibliographic search was carried out using the Cochrane Musculoskeletal Injuries Group Specialised Register, the Cochrane Register of Controlled Trials, Health Technology Assessment (HTA), PEDro, Medline, EMBASE, CINAHL, AMED, DARE, TRIP, and the National Research Register (UK). We searched for meta-analyses (MA), systematic reviews (SR) and randomised controlled trials (RCT) reporting on the use of bisphosphonates in TKA. The search was completed in October 2006. The search terms, selected from the National Library of Medicine's Medical Subject Heading (MESH) database, were: bisphosphonate(s); total knee arthroplasty; TKA; total knee replacement; TKR; total joint arthroplasty; total joint replacement. Two of the authors (SL and RP) appraised the quality of retrieved articles according to standards established by the Cochrane Collaboration [6]. The articles were reviewed in chronological order of publication to identify changes that may have derived from accumulating evidence over the years.

Results

One meta-analysis [7] and two RCTs [8, 9] were retrieved from the literature search (Table 1). One of the RCTs [9] was issued one year after publication of the meta-analysis in 2005. The other RCT [8] was published in 2000 but was not included in the meta-analysis because the latter focused on studies that used dual energy X-ray absorptiometry (DEXA) to measure BMD changes from baseline, whereas the former employed radiostereometry to evaluate the effect of bisphosphonates on implant migration.

The double-blind RCT by Hilding et al. [8] included 50 patients randomised to an intervention or to a control group. Patients in the intervention group received 400 mg clodronate peroral three weeks and six months after cemented TKA. Tantalum beads were inserted into the proximal tibia and into the polyethylene insert at surgery, and radiographs for radiostereometric analysis were taken on the first postoperative day and six weeks, six months and one year after the operation. The accuracy of the radiostereometric analysis was 0.2 mm for translation and 0.3° for rotation. One patient was lost to follow-up. The results of the remaining

Table 1 Studies on the use of bisphosphonates to reduce micromotion and bone loss after total knee arthroplasty

Reference	Type of study	Year	Bisphosphonate	Follow-up	End point of outcome assessment
Hilding et al. [8]	RCT	2000	Clodronate	12 months	Implant micromotion (cemented tibial component as assessed by radiostereometry)
Bhandari et al. [7]	MA	2005	Pamidronate Alendronate	12 months	Periprosthetic BMD variations from baseline (as assessed by DEXA)
Wang et al. [9]	RCT	2006	Alendronate	36 months	Periprosthetic BMD variations from baseline (as assessed by DEXA)

RCT, randomised controlled trial; *MA,* meta-analysis; *DEXA,* dual energy X-ray absorptiometry; *BMD*, bone mineral density

49 patients, as assessed by intention-to-treat analysis, revealed that the clodronate-treated group had significantly less migration (0.29 mm) than the control group (0.40 mm). The authors concluded that their findings support the hypothesis that early postoperative migration is related to bone resorption and that, since late loosening is related to early migration, six months of postoperative clodronate may decrease the risk of late aseptic loosening.

The meta-analysis by Bhandari et al. in 2005 [7] included English and German language articles published from January 1966 to August 2003. The inclusion criteria restricted the choice of papers to RCTs; a quality assessment of the retrieved studies was conducted by the authors. Source of funding of the included studies was also evaluated and the authors also disclosed funding from commercial entities. The meta-analysis included six studies on BMD variations as assessed by DEXA in the periprosthetic bone from baseline up to the 1-year follow-up between a control and an intervention group following total joint arthroplasty (hip and knee replacement). The sample sizes of the trials ranged from 13 to 96 patients. Two of the six studies investigated BMD changes in cemented TKA, six and twelve months after treatment; the other four studies regarded total hip arthroplasty (THA). Alendronate (10 mg/day) was the bisphosphonate used in five studies, whereas pamidronate (one-time intravenous infusion of 90 mg in 500 ml saline solution on the fifth post-operative day) was used in another trial. In all six RCTs, a BMD reduction was observed in both control and intervention groups three months after surgery, although the BMD at the periprosthetic bone level in the bisphosphonate-treated group was significantly higher than in controls. The results of all studies favoured bisphosphonate treatment as opposed to no treatment at the twelve-month follow-up. At the six-month follow-up, the BMD differences between intervention and control groups were greater in studies on TKA than on total hip arthroplasty, but there was no significant difference between the two types of studies at one year. Finally, at the twelve-month follow-up, BMD was significantly higher in patients who received cemented implants than in those who underwent uncemented arthroplasty. However, patients treated by cemented joint replacement were significantly older than those who received uncemented implants. The authors concluded that, because of limitations of available studies and lack of correlation of relevant findings with clinical outcomes such as function, quality of life and revision rates, current evidence on the role of bisphosphonates in reducing periprosthetic BMD should be interpreted with caution.

The RCT by Wang and associates [9] published in 2006 enrolled 60 female patients undergoing cemented TKA who were randomised to receive either peroral alendronate (10 mg/day) for six months after surgery or no medication at all. BMD at the femoral and tibial levels was assessed by DEXA, six, twelve and thirty-six months after surgery. Three patients withdrew from the study because of gastrointestinal intolerance to the drug and three patients were lost to follow-up. This left twenty-nine patients in the treatment group and twenty-five in the control group. DEXA analysis showed that BMD in the distal part of the femur was significantly greater at the six- and twelve-month follow-ups in the intervention group as opposed to controls. However, at the three-year follow-up, BMD had declined and there was no longer a significant difference between the treatment and control groups. A similar trend in BMD variations was recorded at the proximal tibial metaphysis level. The authors concluded that the effect of alendronate on BMD after cemented TKA seems to subside after therapy discontinuation.

Discussion

Two main scenarios underlying early micromotion and late loosening of implant components in TKA have been hypothesised in the literature.

The first, advocated by Hilding and associates [8], stems from the assumption that the uppermost layer of the distal femoral and proximal tibial metaphyses is probably avascular and necrotic due to capillary damage by saw cutting, high-pressure lavage and cement-related toxic trauma (Fig. 1). Since necrotic bone seems to undergo remodelling without resorption being coupled to new bone apposition), the trabeculae may weaken and break-down before osteogenesis starts. Secondary stability by osteointegration may consequently be hindered, with the subsequent development of a fibrous membrane facilitating early micromotion. Microinstability may in turn induce osteolysis because of a fluid-pressure effect and because of debris that becomes trapped within the membrane. This cascade of events would occur in the early postoperative period, i.e. most migration would take place within the first six weeks after surgery and continue at a slower rate up to one year.

The second scenario, based on biomechanical analyses [2], relates to the stress-shielding effect induced by the implant components. Stress-shielding-induced structural weakening of the periprosthetic trabeculae would initiate bone fatigue following cycling loading. This event is thought to take place within the first year after surgery. It may also be assumed that both bone resorption and stress-shielding contribute to early micromotion and late aseptic loosening (Fig. 2).

Bisphosphonates are a class of pharmacological agents capable of inhibiting osteoclast-mediated bone resorption [10]. They are synthetic analogues of inorganic pyrophos-

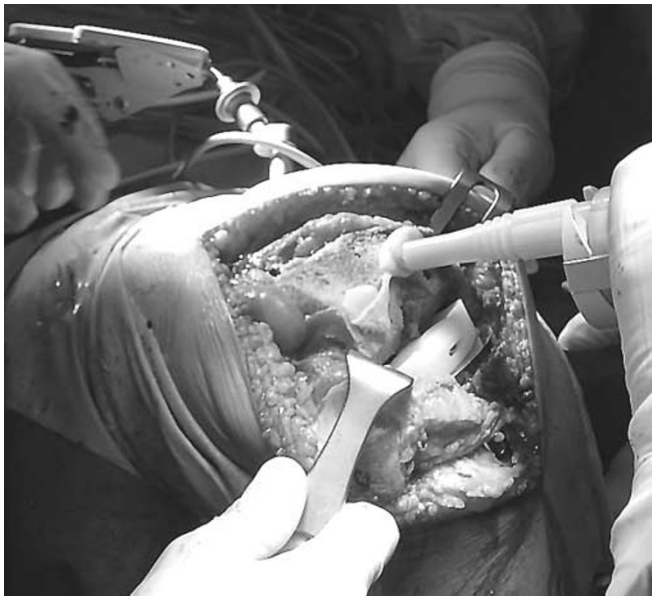

Fig. 1 During bone cutting and high-pressure lavage, thermal and mechanical damage to bone cells and capillaries may occur and may further be compounded by the exothermal reaction of cement setting. Since the resorption of necrotic bone is not coupled to bone apposition, similarly to what takes place in avascular necrosis, ensuing early micromotion can hinder osteointegration and lead to the development of a fibrous membrane and implant subsidence. Fluid-pressure effect and debris pumped into the fibrous membrane during joint motion may add to microsintability and contribute to late aseptic loosening

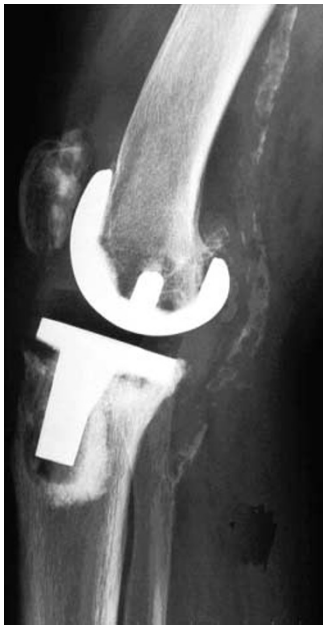

Fig. 2 Many variables are implicated in the development of late aseptic loosening. The combination of prosthetic component micromotion and reduced BMD of the trabeculae surrounding the implant is thought to be an early initiator of a cascade of events, ultimately leading to bone stock loss and gross implant instability, as shown on the radiograph. Current evidence suggests that the off-label administration of bisphosphonates counteracts both adverse mechanisms for one year but the effect on the rate of late aseptic loosening remains to be assessed in long-term follow-up studies

phate wherein the P-O-P bond has been replaced by a non-hydrolysable P-C-P bond. The absence of enzymes capable of splitting the P-C-P bond accounts for their metabolic longevity. Bisphosphonates can be grouped into two major classes according to the type of side-chain substituents linked to the carbon compound: nitrogen-containing and non-nitrogen-containing molecules [10]. The mechanism of action varies between the two classes.

Nitrogen-containing bisphosphonates, such as clodronate and etidronate, are metabolised into non-hydrolysable analogues of adenosine triphosphate (ATP), which are cytotoxic. During the cycle of bone resorption, ATP analogues accumulate within the osteoclasts, whose function is thus inhibited. Non-nitrogen-containing bisphosphonates, such as pamidronate, zoledronic acid, alendronate and risedronate, are thought to interfere with the mevalonate pathway, which is involved in cholesterol biosynthesis. Under physiologic conditions, the mevalonate pathway generates cholesterol precursors that transfer their lipid groups to the cysteine residue of a signalling protein, called GTPase, that regulates osteoclast activity. This biochemical process, named protein prenylation, is inhibited by this class of bisphosphonates and osteoclast regulation is consequently impaired. It should be pointed out that the mechanism of action of non-nitrogen-containing bisphosphonates is not limited to osteoclasts and that the long-term effects on other cell types need further investigation [10].

Thus, it appears that the rationale for the use of bisphosphonates in TKA is related to their capacity of either delaying resorption of necrotic bone early after surgery (thus preventing implant components from subsiding into trabecular bone before new bone is formed) or increasing periprosthetic BMD during the first postoperative year (thus buffering periprosthetic bone against stress-shielding).

Does the evidence support the hypothesis that bisphosphonates play a beneficial role in implant longevity in TKA? The answer is not straight-forward.

The RCT by Hilding et al. [8], which found that a three-week preoperative and six-month postoperative course of peroral clodronate reduces micromotion of the cemented tibial component up to one year after surgery, suggests that this type of bisphosphonate may be effective in preventing the development of a periprosthetic fibrous membrane. However, aseptic loosening is affected by a variety of variables and long-term RCTs are needed to determine whether bisphosphonates can reduce the rate of aseptic loosening.

The meta-analysis by Bhandari et al. [7] supplies evidence that a course of peroral alendronate or a single intravenous dose of pamidronate on the fifth postoperative day counteracts the decline of periprosthetic bone loss observed in controls up to one year after operation. Unfortunately, the short follow-up of the studies included in the meta-analysis precludes any extrapolation regarding the capacity of bisphosphonates to reduce the rate of aseptic loosening in TKA. Two interesting findings of this meta-analysis deserve further discussion. The first regards the seemingly more beneficial effect of alendronate in TKA than in THA. This may ensue from the greater contact of trabecular bone to TKA implant components than to those of total hip arthroplasty, considering that trabecular bone is more susceptible to osteoclastic resorption [7]. The second findings concerns the more pronounced effect of alendronate in cemented implants than in uncemented implants. Although the older age of patients undergoing cemented joint replacement may have been a confounder [7], it is also possible that cement itself accounts for this effect by a dual mechanism. First, cement particles increase the synthesis of pro-resorptive cytokines when cultured in vitro with macrophages [11] and also induce the differentiation of pro-osteoclastic cells to osteoclasts [12]. Second, since uncemented implants are thought to promote periprosthetic BMD by improving stress transfer to trabecular bone, the effect of bisphosphonates may go undetected [7]. However, a two-matched cohort study has recently failed to demonstrate periprosthetic BMD difference between cemented and uncemented fixation of the same type of implant for TKA [13].

Finally, the RCT by Wang et al. [9] conveys important information by showing that the effects of a 6-month course of alendronate on periprosthetic BMD were time-dependent and were lost at the three-year follow-up. This finding indicates that the optimal duration of alendronate therapy required to stably prevent periprosthetic bone loss has yet to be determined.

In conclusion, implant micromotion and stress-shielding-related periprosthetic bone loss in TKA, both potentially contributing to late aseptic loosening by different and probably synergic mechanisms, seem to be counteracted in the short term by a six-month postoperative course of bisphosphonates. The available evidence is limited to the bisphosphonates clodronate, alendronate and pamidronate. The protective effect on periprosthetic BMD appears to diminish over time as no significant difference in BMD was observed between treated patients and controls after three years. Further studies are needed to define the optimal duration of therapy and to determine whether newly marketed higher-dose, weekly or monthly administered bisphosphonates achieve similar protective effects. Whether bisphosphonates can decrease the current rate of late aseptic loosening after TKA has yet to be proven. Although these molecules are promising, we believe that the off-label use of bisphosphonates in TKA remains a therapeutic option open to further clinical research.

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