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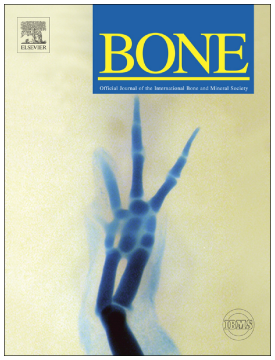

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The use of bisphosphonates to meet orthopaedic challenges

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Abstract

The anti-resorptive properties of bisphosphonates have been explored to manage several conditions that traditionally have required a surgical solution. In osteonecrosis, their use is predicated on the principle that bone collapse occurs during the revascularisation phase of the disease. If the associated resorptive activity were modulated, the resultant preserved joint architecture may improve clinical outcome and reduce the need for joint replacement. Pre-clinical and small-scale clinical studies have given non-conclusive support for this principle. Adequately powered clinical trials with relevant long-term endpoints are still required to firmly clarify the clinical efficacy of this treatment. Several clinical studies have shown that bisphosphonates can reduce periprosthetic bone loss and, in some situations, enhance implant fixation in the early period after joint replacement. This may be advantageous in settings where osseointegration is problematic. However, the ultimate goals of their use in joint replacement has been to reduce the incidence of late periprosthetic inflammatory osteolysis, the main cause of prosthesis failure. Population-based observational studies have associated bisphosphonate use with a lower incidence of revision surgery, supported by pre-clinical data. However, clinical trials have, to date, failed to demonstrate any efficacy for the human disease. The timing of bisphosphonate administration for secondary prevention after acute osteoporotic fracture has been subject to extensive investigation, with pre-clinical studies showing increased callus formation but decreased remodelling and no effect on the restoration of mechanical integrity of bone. Meta-analysis of clinical trial data indicates that early administration of bisphosphonate after acute fracture does not adversely affect fracture union, pain or functional outcomes. Finally, bisphosphonates have also been explored as a treatment for complex regional pain syndrome type-I. A recent meta-analysis has shown a beneficial effect on visual analogue scale pain scores, but an increase in mild adverse events.

Keywords (max 6)

Bisphosphonate, osteonecrosis, implant fixation, osteolysis, fracture healing, algodystrophy

1. Introduction

Bisphosphonates are potent bone anti-resorptive agents that have become the mainstay of treatment for post-menopausal osteoporosis and other conditions associated with pathological bone loss and increased bone turnover. The effect of bisphosphonates for inhibiting osteoclast activity has also made them of interest as a possible solution for diseases that are usually treated by orthopaedic surgery [1-5]. Their use has also been explored to treat conditions that arise as an adverse effect of orthopaedic surgical intervention [6]. In this article, the rationale and current evidence base for the use of bisphosphonates for orthopaedic surgical indications in common, benign, bone and joint diseases is reviewed. The adverse effects of bisphosphonate use that may present to orthopaedic surgeons, such as atypical femoral fractures, are not covered as they are addressed elsewhere in this series.

2. Osteonecrosis

Osteonecrosis, also termed avascular necrosis, describes bone deformity or collapse due to bone cell death that may result in pain, loss of function and joint degeneration (Figure 1). The hip is the most commonly affected joint (followed by the shoulder and knee), with an incidence in UK adults of approximately 3 per 100,000 [7]. Avascular necrosis of the femoral head is also relatively common in the paediatric population, with an incidence of up to 29 per 100,000 in children under the age of 15 years [8]. Adult osteonecrosis may be broadly classified into traumatic (fracture-associated), in which the condition follows disruption of the blood supply to the affected bone, and atraumatic (non-fracture associated) aetiologies. The pathophysiology of atraumatic osteonecrosis remains incompletely understood, but is thought to involve local vascular damage to bone resulting in osteocyte death [9], and in the setting of glucocorticoid-induced osteonecrosis - primary osteocyte apoptosis resulting in disrupted mechanosensing and architectural collapse [10]. Architectural degradation occurs during the revasularisation phase of the disease and is characterised by subchondral bone collapse and remodelling [11-13]. Risk factors for atraumatic osteonecrosis include male sex, corticosteroid exposure, alcohol use, lipid storage disorders, connective tissue diseases (Lupus), vasculitis, and some heritable haemoglobin and coagulopathies [7, 9, 14]. The principle upon which bisphosphonates have been studied as a potential treatment for osteonecrosis is that preservation of bone architecture during the revascularisation and remodelling phase may prevent degeneration of the joint and the need for joint replacement.

Pre-clinical studies

Many pre-clinical studies have been conducted to test this principle. Astrand and Aspenberg [15], using a bone chamber model in rats, showed that systemic treatment with alendronate resulted in new bone formation upon a retained frozen structural bone graft template. In a rat model of surgically induced osteonecrosis [16], Little et al found that animals treated with subcutaneous zoledronate had a substantially lower incidence of femoral head asphericity (13% versus 71%, $p<0.05$) and 34% higher ($p<0.01$) femoral head bone mineral density (BMD) versus saline-treated animals. The zoledronate treated animals also had a higher trabecular number and bone volume but a lower bone formation rate than the saline-treated animals ($p<0.05$, Figure 2). Other investigators have since reported similar findings in other animal models using various bisphosphonates (ibandronate, zoledronate, alendronate). In a meta-analysis of 16 animal studies published up to January 2017 [17], Li et al found that the bisphosphonate treated animals showed a significant improvement in epiphyseal quotient (ratio of femoral head height to width through head centre and expressed as a percentage) with a mean difference of 15.32% (95% confidence interval (95% CI) 9.25 to 21.39). Bisphosphonate-treated animals also had higher bone volume (standardised mean difference (SMD) 1.57; 95% CI 0.94 to 2.20), trabecular number (1.30; 0.80 to 1.79), trabecular thickness (0.77; 0.10 to 1.43) and trabecular separation (−1.44; −1.70 to −0.58) versus the placebo-treated animals.

Combination therapy of a bisphosphonate with an anabolic agent has also been explored as a treatment for osteonecrosis. The rationale for use of bone morphogenetic proteins, and in particular BMP-2, is the upregulation of NF-κB and TGF-β signalling leading to increased angio, chondro and osteogenesis [18-20], whilst the bisphosphonate inhibits resorption of the necrotic bone template. Kim et al [21], in a study of surgically-induced osteonecrosis of the femoral head in piglets, demonstrated that intra-osseous local administration of BMP-2 and ibandronate to the osteonecrotic femoral head resulted in increased (mean ± standard deviation) bone volume versus bisphosphonate only treatment (BV/TV% = 19.7±6.5 versus 11.8 ± 3.7, $p=0.02$). The combination

therapy group also had an increased trabecular number (2.3 ± 0.7 per versus 1.1 ± 0.6, p<0.001), but no difference in epiphyseal quotient.

Clinical studies

To date, several non-randomised cohort studies and randomised clinical trials of small sample size have been conducted to explore the role of bisphosphonates in treating osteonecrosis. Two meta-analyses of clinical trials conducted to date have also been published. Agarwala et al reported the first use of alendronate in osteonecrosis in a case series of Indian patients with osteonecrosis of the hip treated with oral alendronate 10mg/day plus calcium and vitamin D supplementation [22, 23]. In 2005 they reported the 3 month to 5 year results of this intervention in a series of 60 patients [24], reporting improved pain and disability scores, and a stabilisation in radiographic severity of disease. Subsequent to the reported success of early, uncontrolled patient series, several clinical trials of bisphosphonate therapy have been conducted, together with 3 systematic reviews [25-27] and 2 meta-analyses [17, 28] of trials conducted to date. In the most recent meta-analysis Li et al [17] examined 7 clinical trials reported between 2005 and 2016. Pooled results of pain score across 4 studies totalling 277 patients and Harris Hip Scores across 5 studies totalling 329 patients showed that bisphosphonate (oral alendronate in all studies except 1 that used intravenous zoledronate) resulted in a trend towards better scores that did not reach statistical significance (p=0.1 and 0.17, respectively). Similarly, in pooled data totalling 420 subjects there was a trend towards a reduced rate of progression towards head collapse (Relative Risk=0.55, 95% CI 0.26 to 1.16, p=0.012), with a similar non-significant trend towards reduced progression to joint replacement. Of note, although the heterogeneity of the results was generally low for pain, that for head collapse indicated significant heterogeneity between study outcomes in both random and fixed effects models (I^2=77%). To date, the outcomes of the systematic reviews and meta-analyses all conclude that there is currently insufficient evidence to justify the use of bisphosphonates for this indication outside of clinical trials. In the paediatric setting there is also a major ongoing effort to evaluate bisphosphonate use, with clinical trials ongoing [29].

3. Joint replacement

The goal of bisphosphonate use in the setting of joint replacement is to extend the service life of the prosthesis. The intended benefits are reduction in the rate of complications that are associated with loss of periprosthetic bone, including osteolysis, implant loosening, and periprosthetic fracture. Progress in exploring these potential applications are outlined under separate subheadings below.

3.1 Prosthesis fixation

Stable prosthesis fixation to the adjacent bone is an essential prerequisite for the long-term survival of the prosthesis [30]. Joint replacement implants may be fixed to the bone using bone cement (cemented fixation) or through a press-fit with subsequent bone ongrowth to the implant surface (cementless fixation). The process of new bone formation at the implant surface may be considered analogous to that of callus formation. Studies using a technique called radiostereometric analysis that cross references the position of the implant to that of defined landmark points on the bone using simultaneous orthogonal radiographs has allowed measurement of implant migration with an accuracy of within 0.1mm [31]. Use of this technique has shown that excessive early implant migration (>1mm per year over the first 2 years) resulting from poor initial implant fixation is associated with early prosthesis failure [32-36]. Other methods using digitised radiographs to measure prosthesis migration are also described, the most common of which is EBRA, which provides a planar representation of the 3-dimensional migration events [37, 38]. Although these

other methods are less sensitive than RSA, similar migration thresholds for predicting revision risk are described [36-40]. More recent studies have given insights on more sensitive metrics for defining migration risk thresholds appropriate to different classes of prosthesis through association of small scale migration data with large scale prosthesis survivorship data [41, 42], large scale early migration and late outcome data in the same patient populations required to establish causal threshold inference is lacking. Nonetheless, these studies show that less migration is associated with better survival for all prostheses, and that where the migration performance of a specific prosthesis brand within its prosthesis class is greater than that expected, poorer prosthesis survival can be expected.

Whilst the underlying biological mechanisms that modulate early prosthesis migration remain to be clarified, several investigators have explored the possible role of bisphosphonates in enhancing prosthesis fixation, both for cemented and cementless methods. The principle behind both is to prevent osteoclast-mediated bone resorption at the bone surface that occurs because of thermal or mechanical surface damage and osteocyte death incurred as a result of the insertion process [43, 44]. This anti-resorptive activity is intended to maintain the integrity of the implant or cement - bone interface whilst allowing bone modelling once microvascular integrity is restored.

Pre-clinical studies

Both systemic and local administration routes have been explored to examine the effects of bisphosphonates on implant fixation. In one of the earliest studies, Mochida et al [45] demonstrated that repeated dosing of oral alendronate over 26 weeks did not adversely affect early bone apposition to hydroxyapatite-coated hip replacements in a randomised study of 12 dogs, concluding no adverse effect of bisphosphonate therapy on histological implant fixation. Vohra et al [46], in 2014 systematically reviewed 15 animal studies examining the role of ibandronate, zoledronate or alendronate on implant osseointegration in the long bones of ovariectomised animals and found that in 12 of these studies systemic bisphosphonate delivery increased bone volume-trabecular volume ratio and bone implant contact, in 2 studies no benefit was demonstrated, and in 1 the effect was to reduce osseointegration. In a study of ovariectomised rats, Chen et al compared the effects of systemically administered alendronate, zoledronate or strontium ranelate versus placebo on the osseointegration of tibial implants over 12 weeks [47]. They found that all active treatments improved peri-implant BMD, bone-implant contact, and implant push-out strength versus control, and that zoledronate was more effective for these endpoints than either alendronate or strontium ranelate.

In a meta-analysis of 18 animal studies with endpoints measured at up to 24 weeks, Kellesarian et al [48] found that local alendronate administration, applied topically to the bone or implant surface, enhanced bone implant contact, new bone formation, bone volume/trabecular volume ratio, and biomechanical strength of the implant-bone interface. However, heterogeneity of responses was identified between the studies that may be alendronate dose-related, with 2 studies that used the highest dose reporting a negative effect of the drug.

Clinical studies

Hilding and Apenberg [49], in the first clinical trial in 50 cemented knee replacement patients randomised to oral bisphosphonate found that daily oral clodronate (400mg/day) reduced prosthetic migration from 0.40 to 0.29mm ($p=0.01$) over 6 months after surgery. In a study of similar experimental design [50], they later showed that 1mg of ibandronate applied intra-operatively to the local tibial bone surface reduced prosthesis migration from 0.45 to 0.32mm at 6 months, 0.47 to 0.36mm at 12 months, and 0.47 to 0.40mm at 24 months (repeated measures ANOVA $p=0.006$).

However, in a subsequent study [51], the same group found no effect of weekly oral alendronate (70mg/wk) on cementless knee replacement implant migration measured over 2 years.

In the first clinical study of the effect of bisphosphonates on total hip replacement prosthesis migration, Wilkinson et al [52] found no effect of a single dose of intravenous pamidronate (90mg) on acetabular or femoral prosthesis migration over 2 years in a clinical trial of 50 subjects after primary hybrid total hip replacement (cemented femoral implant, cementless acetabular implant). Two further clinical trials have examined the effect of systemic risedronate[53] and zoledronate[54], respectively on cementless femoral prosthesis migration measured by RSA and found no effect of these drugs on prosthesis stability. Friedl et al [55] examined the effect of a single infusion of zoledronate (4mg) on cementless hip replacement migration in a randomised study of similar sample size and found that the drug reduced acetabular implant migration by approximately 4 fold (0.15mm vertical migration versus 0.6mm, $p<0.05$), but did not influence femoral implant migration. Subsequently, Schilcher et al [56] demonstrated that topical administration of ibandronate to the acetabular bone surface immediately before implant cementation reduced implant migration from 0.43mm in the control group (n=30) to 0.20mm in the active treatment group (n=30, p=0.001). Taken together, these studies suggest that bisphosphonate therapy can reduce early acetabular prosthesis migration but probably not that of femoral prostheses.

3.2 Periprosthetic strain adaptive bone remodelling

Mechanosensing within bone is finely tuned to maintain homeostasis at approximately 0.1% strain (1000μStrain) [57, 58]. The elastic moduli of cortical and cancellous bone are 15 and <1.0 GPa, respectively, whilst that of the materials that are commonly used in femoral prostheses are 100 (titanium alloys) to 220 GPa (Cobalt Chrome alloys). Numerous longitudinal clinical studies have demonstrated that a period of strain-adaptive remodelling follows insertion of a hip replacement until a fresh equilibrium within the local strain environment is established. The pattern of local bone loss varies with implant design (Figure 3), but is typically most severe in periprosthetic bone that lies in the proximal medial region of the femur and least in the region adjacent to the tip of the prosthesis, where a small gain in bone mass may occur. These remodelling changes usually occur within the first 12 to 24 months following surgery and are accompanied by a transient rise in biochemical markers of bone turnover. Following these early changes in bone mass, the typical pattern of age related bone loss becomes re-established, resulting in a continued but lower rate of decline in bone mass.

Periprosthetic bone loss is a risk factor for periprosthetic fracture, which has 2 epidemiological peaks, the first in the early months following surgery and second late in the service life of the prosthesis [59, 60]. Whilst there is no established direct causal relationship between early strain-adaptive remodelling or late periprosthetic bone loss and the incidence of such fractures, these events are temporally associated. Periprosthetic bone loss also causes reconstruction challenges at revision surgery.

Numerous clinical studies have been conducted that explore the effect of bisphosphonate therapy on early strain-adaptive bone loss after hip replacement. In the first of these clinical trials [61], Wilkinson et al showed that a single dose of intravenous pamidronate (90mg given 5 days post-operatively) substantially reduced the magnitude of early periprosthetic bone loss at both the proximal femur and pelvis and was accompanied by a suppression in the transient increase in both turnover markers observed in the control group (Figure 4). This effect was most marked in the most proximal and medial periprosthetic bone of the femur, and the effect persisted at 2 years [62], but was lost by 5 years post-operatively [63]. Many other clinical trials of similar design, examining the

effect of other systemically administered bisphosphonates in the setting of both cemented and cementless hip replacement have been conducted since these initial reports. Several systematic reviews and meta-analyses summarising these trials have also been reported [64-69]. Most recently, Shi et al conducted a meta-analysis of 25 clinical trials totalling 1163 participants undergoing hip or knee replacement and followed up to 10 years after surgery [70]. At both the hip and knee site, bisphosphonate administration at doses ranging from once-only to 24 months duration resulted in a higher periprosthetic BMD at up to 10 years post-operatively. The effect was greatest for second and third generation agents and in periprosthetic regions that are most affected by strain-adaptive remodelling. Similar effects on peri-prosthetic bone preservation have been reported recently in 2 clinical trials of RANKL inhibition using denosumab, with broadly similar, but short-lived, effects given the dosing regimes used [71, 72].

3.3 osteolysis and aseptic loosening

Despite advances in prosthetic materials that have improved their wear characteristics and prosthesis survival [73], osteolysis leading to aseptic loosening remains the leading cause for prosthesis failure in England and Wales (NJR 19th Annual report www.njrreports.org.uk). In this process, particulate debris from the implant materials is phagocytosed by host innate immune cells at the prosthesis-bone interface, resulting in proliferation of osteoclast precursors and activation of mature osteoclasts [74]. This increased cytokine activity, in turn, leads to osteoclast differentiation and activation at the interface membrane, resulting in focal periprosthetic osteolysis (Figure 5). This osteolytic activity undermines prosthesis fixation, resulting in aseptic loosening of the prosthesis and/or periprosthetic fracture, giving rise to pain and impaired function and necessitating reoperation. At present there are no established non-surgical treatments for osteolysis. However, given the anti-resorptive action of bisphosphonates, they have been a primary candidate intervention in studies aimed at reducing the incidence of osteolysis and aseptic loosening.

Pre-clinical studies

Shanbhag et al [75], using a previously developed [76] canine model of periprosthetic osteolysis around a cementless THA due to accelerated wear, demonstrated that 5mg daily oral alendronate therapy substantially reduced the incidence of osteolysis (1 of 8 animals developing radiographic osteolysis in the treatment group versus 7 of 8 in the control group). In this model, particles were introduced directly into the prosthesis/bone interface at joint replacement surgery, and alendronate therapy was commenced at day 7 until sacrifice at week 26. This design may not accurately represent the human clinical setting in which debris gradually ingresses into the interface over many years and in whom long-term oral dosing of bisphosphonate may not be appropriate. Millett et al [77], in a study in which polyethylene particles were introduced into the rat knee joint cavity at 4, 6, 8, and 10 weeks after insertion of a loaded tibial hemiarthroplasty, showed that concomitant alendronate infusion (0.01mg/kg/day) prevented particle induced bone loss, whilst later introduction of alendronate treatment at 10 to 16 weeks reversed established bone loss. von Knoch et al [78], in a mouse calvarial model of polyethylene particle-induced osteolysis showed that a single dose of zoledronate at 25μg/kg given at day 4 post particle implantation reduced osteoclast number and midline suture area by approximately 50% at the 14th post-operative day in treated mice versus those that received particles alone ($p<0.05$).

Clinical studies

Several population based registry studies have examined the epidemiological association between bisphosphonate use and the survival of joint replacement prostheses. In the first of these studies,

Thillemann et al [79] examined any bisphosphonate use in a study 16,145 osteoporotic patients with from the Danish Hip Arthroplasty Register. They found that duration of bisphosphonates use up to 120 days, 120 and 240 days, and more than 240 days was associated with adjusted relative risks of revision due to all causes of 2.77 (95% CI; 1.65-4.64), 1.33 (95% CI; 0.63-2.72), and 0.58 (95% CI; 0.32-1.05) respectively. Subsequently, Prieto-Alhambra et al [80] in a retrospective cohort study of primary care data from the United Kingdom found that the rate of hip or knee replacement revision at a mean of 3.5 years follow up following primary surgery in 1912 bisphosphonate users (defined as ≥six prescriptions or ≥ 6months of use) versus that of non-users (n= 41,995) was 0.93% (95% CI 0.52% to 1.68%) versus 1.96% (1.80% to 2.14%). Prieto-Alhambra et al used a similar study design in a subsequent study using the Danish nationwide registries, matching 1.590 bisphosphonate user with 8,966 non-bisphosphonate users and examined the rate of revision hip or knee replacement in these groups. At a median follow up of 2.61 years following primary surgery 1.73% of the bisphosphonate users versus 4.45% of the non-bisphosphonate users had undergone revision surgery (Cox regression hazard ratio 0.41 [95% CI 0.27 to 0.61]).

Whilst these population-based observational studies suggest an association between bisphosphonate use and the rate of early revision surgery after hip or knee replacement, it remains unclear what the signal may mean because of the issue of confounding by indication. Osteolysis leading to aseptic loosening, is a late phenomenon after joint replacement surgery, and rarely occurs within the first 5 years. It does not present within the timescale over which these studies were conducted. Further, osteolysis development is a function of wear debris generation that has its greatest incidence in the young and in males. Osteolysis and aseptic loosening have their lowest natural incidence in post-menopausal females that are also the population in whom bisphosphonate use is most prevalent. Further information on the reasons for revision surgery in these cohorts would thus help clarify the mechanisms of the observed associations. Possible explanations might include enhanced early osseointegration and preservation of periprosthetic bone mass resulting in a lower incidence of early technical (mechanical) failure or periprosthetic fracture.

Few clinical trials of bisphosphonate therapy in the setting of clinically-relevant periprosthetic osteolysis have been reported. Rubash et al [81], in a multi-centre study of 123 subjects with osteolysis after hip replacement, found that daily oral administration of alendronate (35mg) did not affect the progression of established osteolytic lesions over 18 months. In a small clinical trial, Holt et al [82] randomised 10 patients scheduled for revision surgery for osteolysis to receive either alendronate 70mg weekly or placebo over 8 weeks prior to surgery. Samples of the osteolytic membrane taken at the time of revision surgery demonstrated no differences in pro-inflammatory cytokine or RANK, RANKL, or OPG expression between treatment groups. However, no bone samples were taken to examine osteoclast numbers between the treatment groups to determine a biological effect on cell activity. Whilst this study did not examine for such a biological effect, other authors have also observed a lack of efficacy of bisphosphonates in the setting of clinical inflammatory joint disease progression [83-85]. Zhang et al [86] sought to explain the lack of effect of bisphosphonate treatment for structural osteolytic lesions in tumour necrosis factor-transgenic mice that develop erosive arthritis versus wild-type littermates. They found that the anti-apoptotic proteins Ets-2 and Bcl-xl were substantially upregulated in the inflammatory osteolytic environment, and protected the osteoclasts from alendronate-induced apoptosis. In summary, current data does not support the use of bisphosphonates in the treatment or prevention of osteolysis. An alternate strategy, focussed directly on the inhibition of RANKL signalling, is currently underway (NCT01358669) to determine whether denosumab therapy reduces osteoclast activity within osteolytic lesions.

4. Fracture healing

The healing of an acute fracture is a complex process that may be divided into several discrete but overlapping stages. In typical fracture healing by callus formation (indirect fracture healing), an initial inflammatory stage (day 0 to ~day 7) is characterised by haematoma formation, necrosis of the bone ends, soft tissue injury and platelet degranulation in an inflammatory cellular response that is subsequently replaced by granulation tissue. In the repair phase (weeks to months) progenitor cells in the periosteum and endosteum develop into osteoblasts, whilst capillary ingrowth facilitates the chemotaxis of mesenchymal stem cells to the fracture site where they proliferate and differentiate into fibroblasts and chondrocytes, creating a fibro-cartilaginous matrix of soft callus. As the stiffness of the callus increases, it undergoes endochondral ossification to woven bone from the fracture periphery inwards whilst periosteal and endosteal intramembranous ossification continues to form hard callus. The final remodelling stage (months to years) begins once the fracture has united solidly with woven bone. This is slowly replaced to lamellar bone by osteonal remodelling, with eventual restoration of normal mature bone architecture and the medullary canal. In the setting of surgical intervention by rigid internal fixation, the natural fracture haematoma and callus formation process is disturbed and much of the healing process occurs through intramembranous ossification and osteonal remodelling (direct fracture healing).

The timing of the introduction of treatment following osteoporotic fracture in the bisphosphonate-naïve patient has been controversial because of anxiety that inhibition of bone remodelling may impact adversely upon fracture healing, particularly in the setting of surgical fracture fixation. These concerns about the use of and timing of the introduction of bisphosphonates in the setting of acute fracture has precipitated several studies, outlined in the following sections.

Pre-clinical studies

In one early study [87], Peter et al studied the effect of daily oral alendronate (2mg/kg) on surgically-induced mid-diaphyseal radial fracture healing in skeletally mature beagle dogs. They found that callus volume at 16 weeks in alendronate treated dogs was greater than twice that in placebo treated dog. Mechanical load at failure and flexural rigidity of the healing bone was unaffected by alendronate, but callus remodelling was delayed. A subsequent study by Li et al [88], showed that intravenous incadronate (10µg/kg or 100µg/kg) administered 3 times per week for 2 weeks prior to mid femoral fracture and intramedullary wire fixation resulted in greater callus formation at 6 and 10 weeks that was associated with greater ultimate fracture callus strength, and that continuous treatment post fracture at 100µg/kg augmented this effect but also delayed remodelling to lamellar bone. Several subsequent pre-clinical studies using a variety of animal models have shown very consistent findings of a larger fracture callus and remodelling delay, but without impairing the strength of the healing bone [89-92]. These studies were performed across various bisphosphonates and routes of systemic administration.

Clinical studies

Despite the broadly positive data from pre-clinical studies, concern has remained about the safety and timing of the introduction of bisphosphonate therapy after osteoporotic fracture, particularly in the setting of surgical repair of the fracture. Molvik and Khan [93], in a systematic review of 16 clinical studies, mostly retrospective case-control or cohort studies and 3 clinical trials, found that time to fracture union was longer in patients with distal radius fracture but not in those with femoral fractures versus control subjects with fractures at the same sites. No relationship the between timing of bisphosphonate introduction and union time was identified. However, the analysis included a heterogeneous group of studies, of which only 5 measured time to union in both a study

and control group (3 lower limb and 2 upper limb studies) and only 2 were formal clinical trials. Conversely, in a meta-analysis of 8 clinical trials involving 2,508 patients published a year earlier [94], Xue et al found no difference in either short-term (≤ 3 months) or long term (≥ 12 months) indirect bone healing between bisphosphonate infused versus non-bisphosphonate-treated patients. Further, in a systematic review and meta-analysis of 10 clinical trials including 2888 patients [95], Li et al examined the timing of the initiation of bisphosphonates within 3 months after surgery for fracture healing. Patients treated with bisphosphonates had no difference in radiological fracture healing times compared with those in the control group (mean difference 0.47 [95% CI −2.75 to 3.69), and no difference in the rate of delay or non-union of fracture healing (odds ratio 0.98 [0.64 to 1.50]. All of these analyses included many of the same original study populations, all with the exception of 2 [96, 97] included fewer than 100 subjects, and in the largest (HORIZON Recurrent Fracture Trial) [97] treatment was started ≥90 days post surgery, by which time fracture union would be expected.

Most recently, Duckworth et al [98] reported a clinical trial of 421 bisphosphonate-naïve men and women aged >50 years with a radiographically confirmed d fracture of the distal radius and randomized them in a 1:1 ratio to receive alendronate (70 mg/week) or placebo within 14 days of the fracture. This sample size gave a power of 84% (at p=0.05) to detect a pre-specified 15% difference in the proportion of patients who had a healed fracture at 4 weeks post-injury (the pre-defined primary endpoint). Clinical care of the fractures was carried out according to normal clinical practice, and included a similar number of operated versus non-operated (78% versus 22%) patients in each randomisation arm. At 4 weeks, 48 of 202 (23.8%) fractures had united in the alendronate group compared with 52 of 187 (27.8%) in the placebo group (absolute proportion difference 4.0% [95% CI –4.7 to 12.8], p=0.36). There were no differences in the proportion of fractures that had united at any other time point over 6 months post-injury, and no differences in the Disabilities of the Arm Shoulder and Hand questionnaire score, pain at the fracture site, grip strength, or any other clinical outcome (Figure 6). The authors concluded that early administration of alendronate among patients >50 years after acute distal radius fracture is safe and does not affect fracture union or the clinical outcome.

The use of bisphosphonates in the setting of fracture fixation augmentation and in the management of bone defects has been addressed in a previous review [6]. However, it is of interest to note that pin tract problems overshadow the clinical use of external fixation devices in fracture fixation and in their treatment with distraction osteogenesis. Two studies have examined the use of bisphosphonates for this specific problem. Both support the use of bisphosphonate-coated external fixator pins to enhance fixation, particularly at metaphyseal sites [99, 100].

5. Complex regional pain syndrome type 1

Complex regional pain syndrome type 1 (CRPS-1, also known as algodystrophy), is a clinical syndrome of variable course and unknown cause characterised by pain, swelling, and vasomotor dysfunction of an extremity [101]. The condition most commonly arises after upper limb injury or surgery [101]. In a population-based study conducted in a rural county of Minnesota, United States [102], Sandroni et al found an incidence rate of 5.5 per 100,000 person years at risk, and a prevalence of 20.6 per 100,000. The female to male ratio was 4:1 with a median age of onset of 46 years. Although most cases resolve without invasive treatment, the condition runs a protracted course in a persistent minority, and may result in permanent disability [101, 102].

Although the underlying pathophysiology of CRPS-1 is thought to have its basis in autonomic dysregulation [103, 104], early change in bone akin to a regional acceleratory phenomenon [105], is

thought to contribute [106, 107]. Given the increase in bone turnover and bone loss observed in CRPS-1 [108, 109], several studies of bisphosphonate therapy have been conducted in an attempt to alter the natural history of the disease.

Pre-clinical studies

Wang et al [110], exposed animals to placebo or bisphosphonates in a rat tibial fracture model of CRPS. They found that alendronate (60µg/kg/day s.c.) or zoledronate (3mg/kg/day p.o.) for 28 days and started at the time of fracture inhibited the development of hind paw allodynia and reduced hind paw unweighting by 44 and 58%, respectively versus placebo treated animals, but did not reduce paw temperature or oedema. Alendronate treatment also inhibited osteoclast and eroded surface and increased bone volume/trabecular volume versus placebo treatment.

Clinical studies

A modest number of clinical trials of the effect of bisphosphonates on CRPS-1 have been conducted. In a 2009 systematic review of 4 clinical trials involving 118 patients treated with alendronate (n=2 studies), pamidronate or clodronate versus placebo [111]; 2 of the studies showed improvement over 3 months in joint mobility and 1 showed an improvement in SF-36 physical function score. In a more recent systematic review and meta-analysis [112], Chevreau et al identified 4 clinical trials of moderate to good quality comprising 181 patients randomised at 1:1 to receive either bisphosphonate or placebo and in whom the outcome measures included visual analogue scale (VAS) pain scores. They found that bisphosphonate therapy resulted in lower VAS pain scores over 30-40 days (SMD -2.5 [95% CI 11.8 to -3.4, p<0.001)] and at up to 90 days (-2.5 [-1.8 to -3.4], p<0.001). However, the heterogeneity of the results was large (I^2=88%). Although clinical trials of oral zoledronate (NCT02504008) and neridronate (EudraCT 2014 001156-28 and 2014-001915-37) have been registered, results from the latter report no significant effect of 4 infusions of neridronate (250mg) on the primary endpoint of pain intensity score over 12 weeks (https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-001915-37/results).

6. Conclusions

In summary, bisphosphonates have been explored as an alternative to surgery for many diseases that are currently managed by orthopaedic surgeons. In osteonecrosis, pre-clinical data suggests a role in preserving bone architecture, a finding that has been replicated in some cohort studies and clinical trials. However, meta-analysis of the clinical trial data thus far does not conclusively support their use. A large-scale, definitive clinical trial using an appropriately timed, pragmatic bisphosphonate administration schedule and relevant mid-to long term clinical endpoints is still required to confirm their use in this setting. Bisphosphonate treatment can reduce the early migration of joint replacement prosthesis, with an effect that depends on the method of fixation, the specific prosthesis component and context, appears greater with local versus systemic administration and appears to be more effective for knee replacement than hip replacement. Systemic bisphosphonate therapy also has a clear effect on reducing strain-adaptive bone loss that occurs following surgery. The clinical impact of these effects in reducing revision surgery for loosening and periprosthetic fracture remains unclear. Although epidemiological association studies indicate lower joint replacement revision rates in patients receiving bisphosphonates, confounding by indication limits the interpretation of these studies. The few clinical trials of bisphosphonates for the treatment of established periprosthetic osteolysis have failed to demonstrate any benefit, a finding akin to those of their use to prevent periarticular erosions in patients with inflammatory arthritis. Studies in both animals and humans have explored timing of introduction of

bisphosphonates for secondary fracture prevention. These studies show no adverse effect on acute fracture healing, both for surgically and non-surgically treated fractures a various sites. Finally, given bone involvement in CRPS-1, the small number of clinical trials reported to date collectively indicate that bisphosphonate use reduces short and mid-term pain outcomes, although the precise mechanism of action of this effect is unclear.

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Figures

Figure 1. Plain anteroposterior Radiograph of a skeletally mature pelvis showing late-stage osteonecrosis of the left femoral head (arrow).

Figure 2. Representative histological sections of the femoral head from a study of zoledronate treatment of surgically-induced osteonecrosis [16]. A) Saline non-operated, B) saline operated, C) Zoledronate post, and D) Zoledronate pre-post. Tb.N. and BV/TV are reduced in the B) saline-operated femoral heads compared with the C) Zoledronate post and D) Zoledronate pre-post groups. 5µm undecalcified sections stained with 1% von Kossa stain, original magnification x25.

Figure 3. Longitudinal mean pixel bone mineral density change over 2 years around 5 different femoral prosthesis designs measured by Dual-energy X-ray Absorptiometry-Region Free Analysis. The mean distribution of pixel BMD change after 24 months is shown for (a) composite-beam (Charnley), (b) double-taper (Exeter), (c) triple-taper (C-stem), (d) Bi-metric total hip replacement, and (e) ASR hip resurfacing prosthesis designs, respectively.

Figure 4. Action of bisphosphonates on the remodelling transient and measured BMD change after hip replacement. The prosthesis induces a transient increase in the activation frequency of bone remodelling units. The resulting transient expansion of the remodelling space is measured by DXA as a biphasic BMD change response following completion of the remodelling transient.

Figure 5. Overview of the biological response to wear debris. Recruitment and activation of osteoclasts may occur directly through the production of RANKL by fibroblasts, or indirectly through the production of pro-inflammatory cytokines that stimulate the production of RANKL by the osteoblast. TNF may stimulate osteoclast differentiation and activation though both routes.

Figure 6. Clinical outcomes in a clinical trial of alendronate versus placebo on distal radial fracture healing [98]. A) Proportion of subjects with a healed fracture in the alendronate versus placebo group ($P>0.05$ all time points), B) Effect of treatment on the DASH score (mean ± 95% confidence interval, $P>0.05$ at all time points).

Credit author statement

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Highlights

- Bisphosphonates have potential application to several conditions that currently challenge orthopaedic management
- In osteonecrosis, bisphosphonates may preserve bone architecture during revascularisation, and may reduce the incidence of secondary osteoarthritis. Definitive studies are ongoing.
- In joint replacement, early administration of bisphosphonates reduces peri-prosthetic bone loss and can enhance early osseointegration, but a causal role in reducing late osteolysis is not established
- Bisphosphonate initiation after acute fracture does not adversely affect clinical fracture union, pain or functional outcomes
- In complex regional pain syndrome type-I, bisphosphonate use can improve pain scores, although further studies are required to define their role and timing in the disease

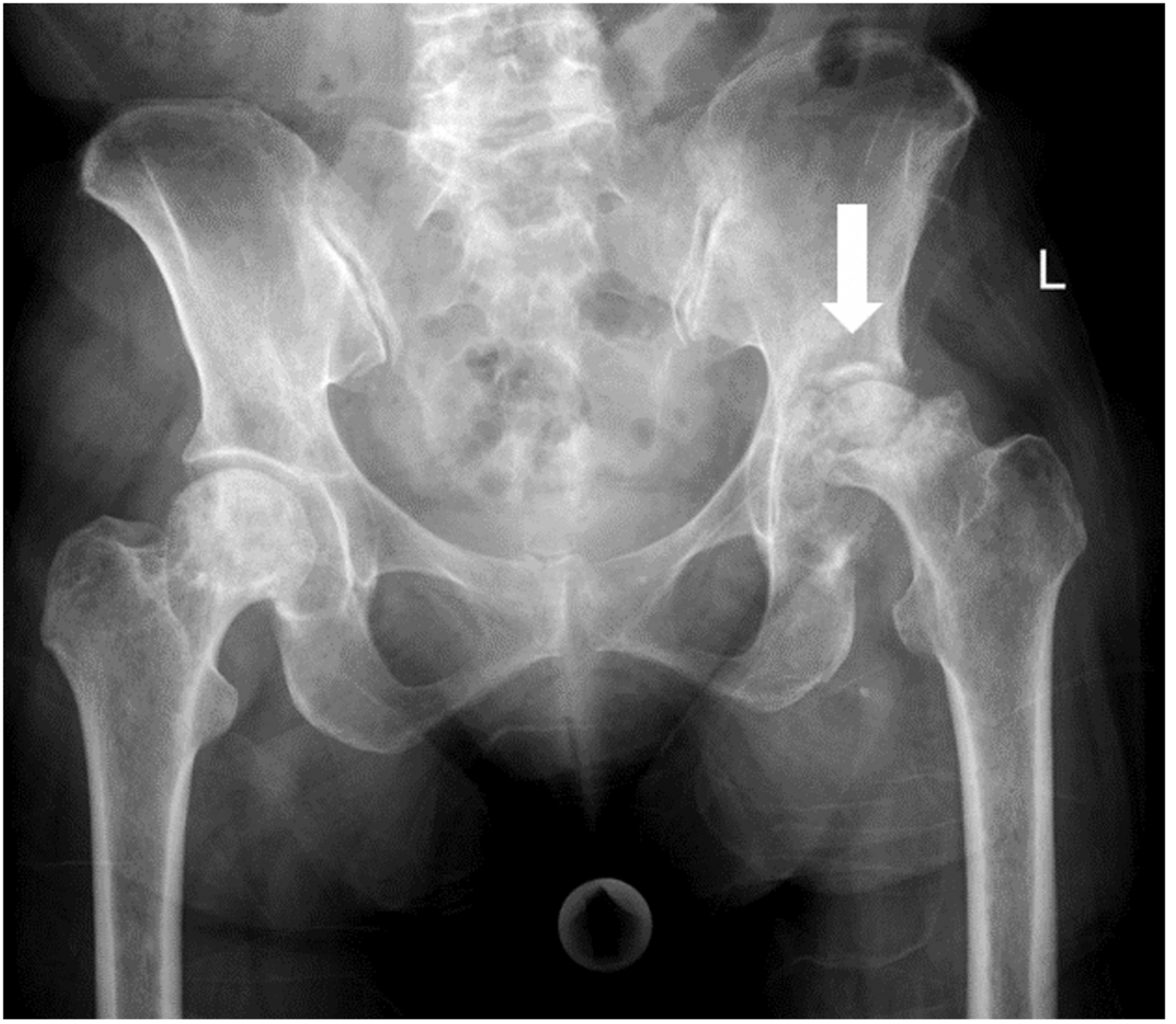

Figure 1

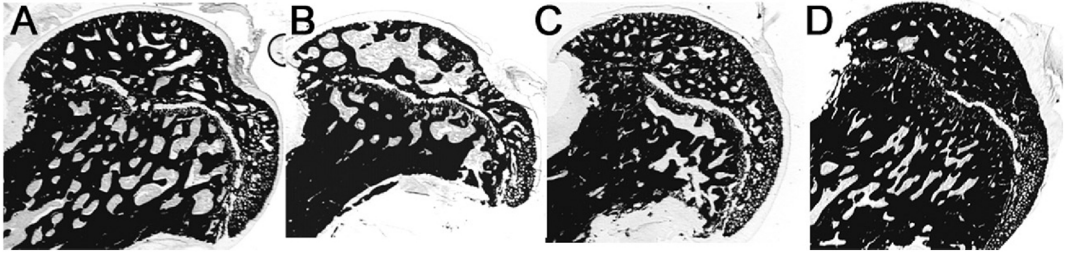

Figure 2

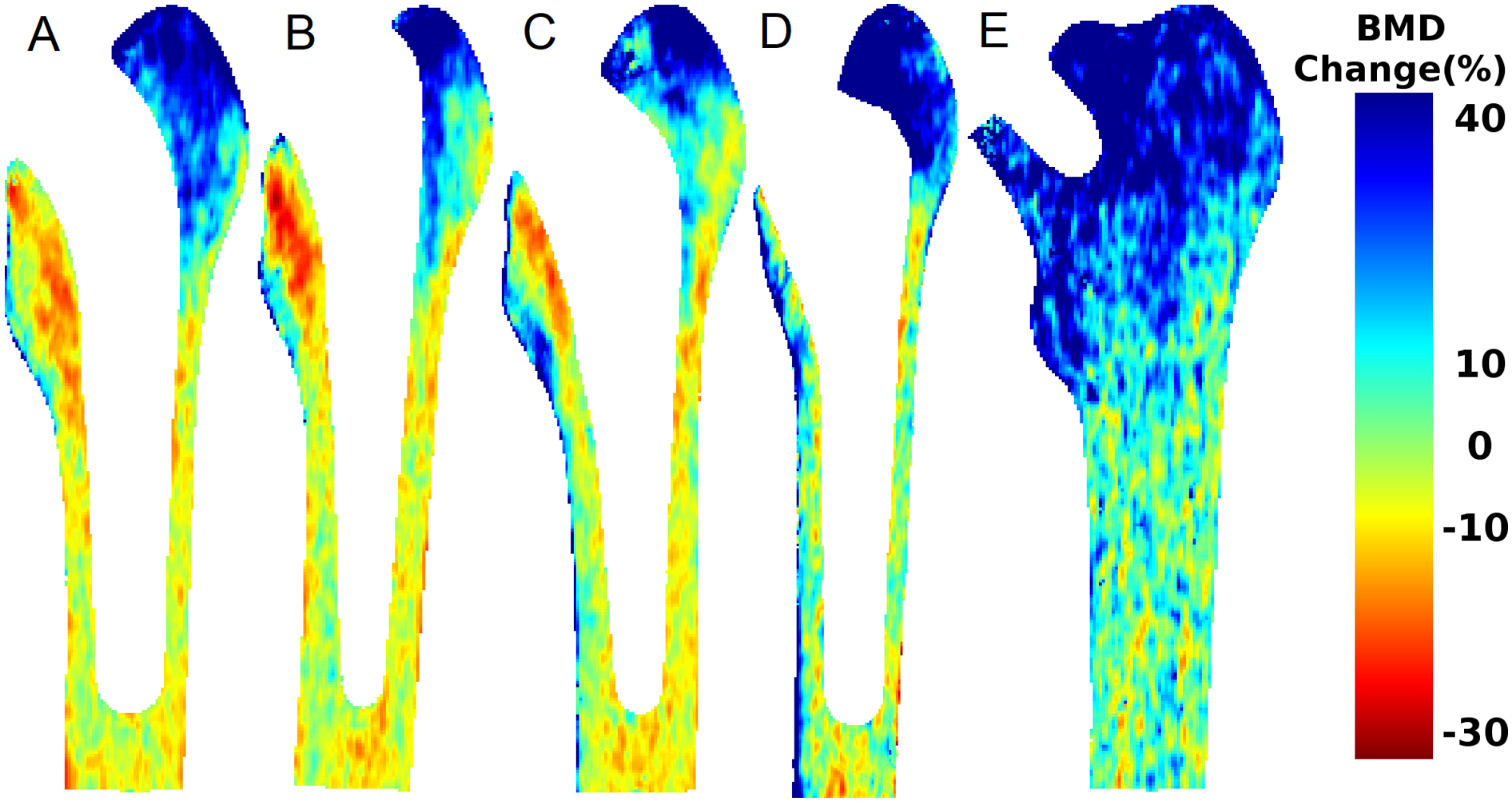

Figure 3

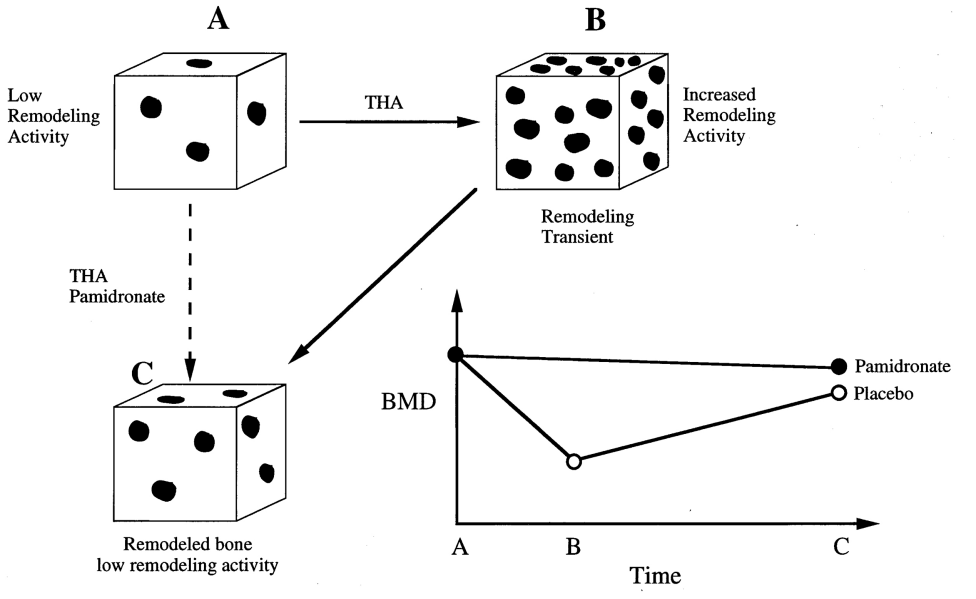
A
B
Low
Remodeling
Activity
THA
Increased
Remodeling
Activity
Remodeling
Transient
THA
Pamidronate
C
Remodeled bone
low remodeling activity
BMD
Pamidronate
Placebo
A
B
C
Time

Figure 4

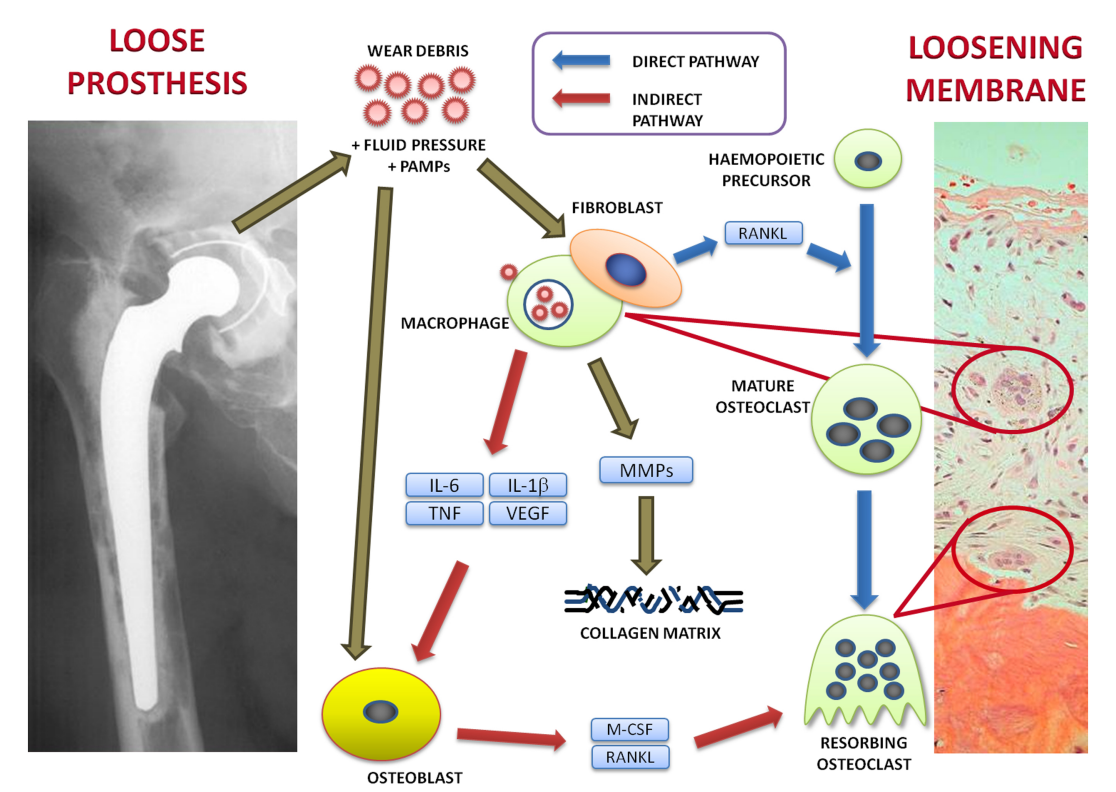
LOOSE PROSTHESIS
WEAR DEBRIS
+ FLUID PRESSURE
+ PAMPs
DIRECT PATHWAY
INDIRECT PATHWAY
LOOSENING MEMBRANE
HAEMOPOIETIC PRECURSOR
FIBROBLAST
RANKL
MACROPHAGE
MATURE OSTEOCLAST
IL-6
IL-1β
TNF
VEGF
MMPs
COLLAGEN MATRIX
OSTEOBLAST
M-CSF
RANKL
RESORBING OSTEOCLAST

Figure 5

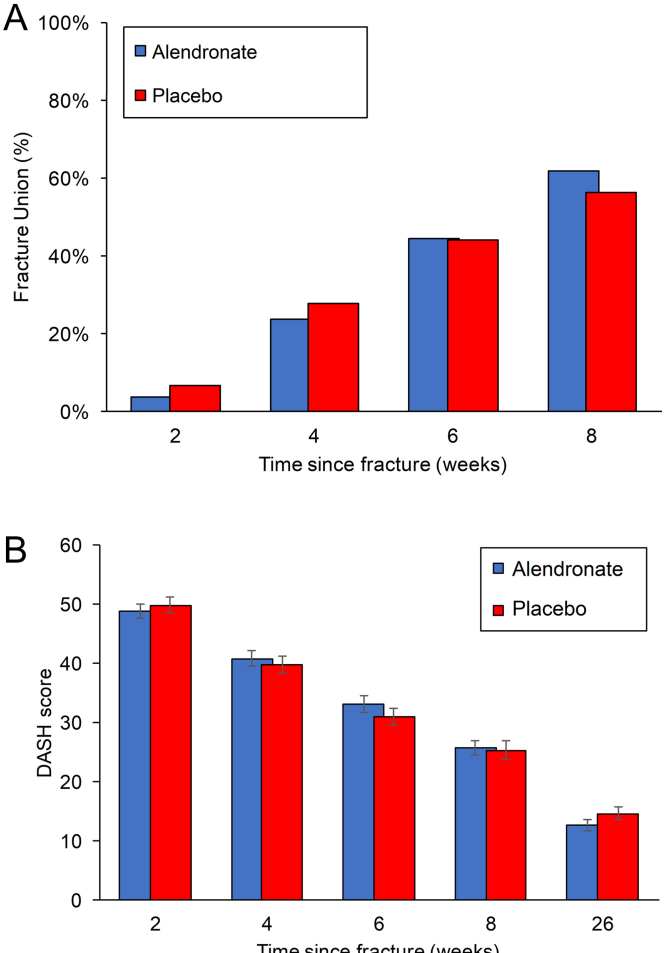
A
100%
80%
60%
40%
20%
0%
Fracture Union (%)
Alendronate
Placebo
2
4
6
8
Time since fracture (weeks)
B
60
50
40
30
20
10
0
DASH score
Alendronate
Placebo
2
4
6
8
26
Time since fracture (weeks)

Figure 6