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Review

Timing of osteoporosis therapies following fracture: the current status

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***Abstract*:** In most patients, osteoporosis is diagnosed only after the occurrence of the first fragility fracture. It is of utmost importance to start osteoporosis medications immediately in these patients to prevent future fractures and also to reduce associated mortality and morbidity. There remains a hesitancy over initiating osteoporotic medications, specifically for antiresorptive agents like bisphosphonates following an acute fracture due to concern over their effect on fracture healing. The purpose of this review is to study the effect of the timing of initiation of different osteoporosis medications on healing after an acute fracture. Most of the human studies, including randomized control trials (RCTs), did not find any significant negative effect on fracture healing with early use of bisphosphonate after an acute fracture. Anabolic agents like teriparatide have shown either neutral or beneficial effects on fracture healing and thus can be started very early following any osteoporotic fracture. Although human studies on the early use of other osteoporosis medications like denosumab or strontium ranelate are very sparse in the literature, none of these medications have shown any evidence of delay in fracture healing. To summarize, among the commonly used anti-osteoporosis agents, both bisphosphonates and teriparatide are safe to be initiated in the early acute post-fracture period. Moreover, teriparatide has shown some evidence in favor of reducing fracture healing time.

Keywords: acute fracture, bisphosphonate, denosumab, teriparatide, timing

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Introduction

Osteoporosis and the consequent fragility fractures constitute one of the most underdiagnosed and undertreated medical conditions, despite its high incidence, morbidity, mortality, and healthcare expenditure.[1,2] In most patients, osteoporosis remains a silent disease until the occurrence of fragility fracture. After the first osteoporotic fragility fracture, the risk of subsequent fracture increases further. Despite the widely available tools for diagnosis and cost-effective medications to treat osteoporosis, a phenomenon of 'treatment gap' has been well reported in the literature.[3] The period following an acute fracture gives an opportunity to initiate medical therapy with anti-osteoporotic agents and reduce the treatment gap in these patients.[4] One of the reasons behind the inertia for the initiation of osteoporosis medications following a fracture is the apprehension regarding the effect of these agents on acute fracture healing. Bisphosphonates inhibit bone remodeling[5] and theoretically can hinder fracture healing.[6] Even osteoporosis itself can negatively impact the fracture healing process.[7] On the contrary, anti-osteoporotic agents like teriparatide have been tried to enhance fracture healing due to its anabolic effect.[8] Following an acute fracture, the optimal timing of starting the osteoporosis medications especially for antiresorptive agents like bisphosphonate remains an important concern. The purpose of this review is to assess the current literature on the effect of timing of initiation of different osteoporosis medications following an incident fracture.

Physiological basis of the effect of osteoporosis therapies on fracture healing

Antiresorptive drugs

Among the antiresorptive drugs, bisphosphonates are the most widely used. Bisphosphonates because of their structural similarity with inorganic pyrophosphate, bind to hydroxyapatite crystals and remain embedded in mineralized bony matrix for prolonged duration. During bony resorption, bisphosphonate gets released and acts by inhibiting farnesyl pyrophosphate synthase (nitrogen-containing bisphosphonates) or by incorporating into the terminal pyrophosphate of adenosine triphosphate (non-nitrogen-containing bisphosphonate), ultimately leading to inhibition of osteoclasts.[5] As a consequence, there is suppression of bone resorption as well as remodeling. This osteoclastic bone resorption plays an important role in fracture repair, specifically in the remodeling phase when the callus is transformed into normal lamellar bone. Thus, there remains a theoretical risk of the impaired fracture healing process with the use of bisphosphonate following an acute fracture.[9] The data from the animal models of bisphosphonate use are not consistent. However, the majority of the animal studies have reported increased callus size,[10–12] increased bone mineral content,[12] increased biomechanical strength,[11] and delayed remodeling[10,13] with bisphosphonate use. Contrary to the theoretical concept, even advanced histological healing has been reported.[11] In an osteoporotic rat model study, which evaluated the fracture healing according to timing of zoledronic acid (ZA) infusion (day 1, week 1, and week 2), no significant difference in radiological healing was reported.[14] Amanat *et al.*[15] have reported an association of larger and stronger callus production with delaying of ZA infusion in a rat fracture model study.

Denosumab is a fully human monoclonal antibody and a receptor activator of nuclear factor-kB ligand (RANKL) inhibitor. It binds to RANKL and inhibits bone resorption by inhibiting osteoclast formation, function, and survival. Murine models[13] have demonstrated that denosumab did not diminish the mechanical integrity of the healing fractures but in contrast, increased strength and stiffness of the fractured bones after 42 days of treatment.

Anabolic drugs

Parathyroid hormone (PTH) and PTH-related protein (PTHrP) are the anabolic agents used in the treatment of osteoporosis. Both act on the PTH1 receptor (PTHR1) leading to activation of downstream signaling pathways with the recruitment and proliferation of osteoprogenitors. The main effect of teriparatide [PTH(1-34)] is to stimulate bone formation without stimulating bone resorption. It promotes fracture healing by multiple mechanisms. It promotes proliferation and differentiation of mesenchymal stem cells, chondroprogenitors, and osteoprogenitors.[16] It also leads to chondrocyte maturation, production of bone matrix proteins, and osteoclastogenesis.[17] Teriparatide also enhances callus formation and remodeling by stimulating the synthesis of bone matrix protein and osteoclastogenesis. Earlier studies have shown that intermittent administration of PTH (1-34) enhances the callus formation and mechanical strength of healing fractures in rat.[18] Significant increases have been noted in the callus area and strength of rats treated with PTH.[19] Kakar *et al.*[20] using a mouse fracture healing model has shown that PTH treatment induced the expression of chondrogenesis-related genes (Sox9, Sox5, Col2a1, and Col10) during the early phase of healing (days 5 and 7) and the expression of osteogenesis-related genes (Runx2 and Sp7) at days 10 and 14. Furthermore, the levels of unphosphorylated nuclear-localized β-catenin increased in osteogenic and chondrogenic cells in the callus of the PTH group, suggesting that the activation of the Wnt signaling pathway is one of the mechanisms responsible for the promotion of fracture healing.

Abaloparatide is a synthetic 34-amino acid peptide and a selective activator of PTHR1. It has 41% homology to PTH (1-34) and 76% homology to PTHrP. Bernhardsson and Aspenberg[21] compared the effect of abaloparatide *versus* teriparatide on fracture healing in mouse models. Both drugs seemed to improve fracture healing. In another recent study in rats with femoral fracture, treatment with abaloparatide resulted in greater callus area and volume, higher bridging scores, and greater callus maximum load and stiffness *versus* vehicle controls.[22]

Effect of timing of therapy on fracture healing

Antiresorptive drugs

Among the different antiresorptive agents, studies in the literature on fracture healing are limited to only bisphosphonates and denosumab.

Bisphosphonates. As the purpose of this review is to study the effect of timing of initiation of anti-osteoporotic drugs following a fracture, only the studies that evaluated the impact of initiation of bisphosphonate therapy in the acute post-fracture period (<4 weeks) are discussed in this section. In most of the studies available in the literature, early initiation of bisphosphonate had been compared with either placebo or control. However, in a few studies the patients were compared according to the time of initiation of bisphosphonate (early *versus* late). Alendronate, ZA, and risedronate were the most common bisphosphonates studied in the literature. These trials evaluated the effect of bisphosphonate therapy on all the common fracture sites including hip, distal arm, humerus, lower leg, as well as spinal surgeries.

Effect on hip fracture. Among the six studies that evaluated the effect of bisphosphonate on the healing of hip fractures, all but one were randomized controlled trials (RCTs). In the multicenter, double-blind RCT by Colón-Emeric *et al.*[23] (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly Recurrent Fracture trial), a total of 2127 patients with low-trauma hip fracture were randomized to either receive intravenous ZA 5 mg ($n=1065$) or placebo ($n=1062$). There was no difference in the incidence of delayed fracture healing between ZA and placebo arms (odds ratio [OR], 1.17; 95% confidence interval [CI], 0.72–1.90; $p=0.61$). The patients in the ZA arm were subdivided according to the timing of ZA infusion following the day of surgery as follows: within 2, 2–4, 4–6, and >6 weeks. There was no statistically significant difference in the incidence of delayed fracture healing in the subgroups according to the timing of ZA infusions with respect to the placebo (OR: 0.19, $p=0.10$; OR: 0.78, $p=0.67$; OR: 1.80, $p=0.20$, and OR: 1.48, $p=0.29$; respectively). Analysis by logistic regression model also did not reveal any association between timing of ZA infusion following surgery and delay in fracture healing ($p=0.44$). One of the major limitations of this study was a relatively small number of patients (ZA: 56, placebo: 46) in the subgroup within 2 weeks. However, both the total number of included patients and those in other subgroups were much higher than any other available studies evaluating the effect of timing of bisphosphonate on the healing of the fracture. Lack of universally accepted criteria for delayed hip fracture healing and heterogeneity due to differences in performed surgical interventions were other limitations of this study. In a prospective multicenter RCT from Korea, a total of 77 patients with osteoporotic intertrochanteric fractures were randomized according to the timing of initiation of alendronate therapy following surgery as follows: group A (after 1 week), group *B* (after 1 month), and group C (after 3 months).[24] The authors did not find any significant difference in radiological healing among the 3 groups (A: 10.7 ± 4.4 weeks, B: 12.9 ± 6.2 weeks, and C: 12.3 ± 7.1 weeks; $p=0.42$). However, though statistically not significant, a trend toward earlier healing was found in group A and all the fractures in this group were healed earlier (by 20 weeks) following surgery. There was no difference in functional outcome between the groups after 1 year of surgery as assessed by Koval classification. Although this study had limitations of small sample size, lack of control group, and heterogeneity in the use of surgical implants, its findings refute any delay in fracture healing due to early use of bisphosphonate after surgery. In another RCT by Li *et al.*,[25] 60 elderly intertrochanteric fracture patients treated with proximal femoral nail anti-rotation surgery, were divided randomly to receive either intravenous ZA (5 mg) or control group. All the patients additionally received calcium and vitamin D and were followed up for 1 year.[25] The mean fracture healing time was significantly lower in the ZA group (13 ± 3.2 weeks) than in the control group (15 ± 4.6 weeks) ($p=0.02$). Moreover, patients in ZA group had reported significantly higher QOL (as assessed by the Osteoporosis Quality of Life Scale) at the end of 1 year of follow-up ($p=0.04$). However, there was no significant difference in the Harris hip joint function score or pain score between the two groups. In the study by Sargin *et al.*,[26] a total of 73 patients with osteoporotic intertrochanteric fracture were enrolled. Among them, 50 patients who had proximal femoral nail surgery were randomized into two groups according to time of ZA infusion (group 1: within 1 week, group 2: within 1 month). There was no significant difference in radiological healing as assessed by the RUSH (Radiographic Union Score for Hip) score between the two groups. By 6 months follow-up time, all the fractures in both groups got united and there was no significant difference in functional score between the two groups. Moreover, bone mineral density (BMD) and T score were significantly improved in both groups at the 1-year follow-up (from the baseline), indicating

the benefits of ZA infusion. In a recent RCT by Jalan *et al.*,[27] healing of intertrochanteric fracture was compared according to time of ZA infusion. A total of 123 patients were randomized to three groups: ZA infusion within one week (Group 1a: 41 patients), at 6 weeks (Group 1b: 42 patients), and control (Group 2: 40 patients). There was no significant difference in fracture healing time (Group 1a: 13.7 ± 2.8, 1b: 13.7 ± 3.5, and 2:14.2 ± 2.8 weeks) among these groups ($p = 0.69$). At the end of 12-months' follow-up, the functional outcomes were also similar between the groups. In an observational study, 43 osteoporotic patients with intertrochanteric fracture were given IV ZA within 1 week of surgery. There was no control group in this study, but all the fractures showed radiological signs of union by 6 months of follow-up.[28] To summarize, these studies did not find any significant delay in the healing of hip fracture with early introduction of bisphosphonate therapy.

Effect on distal radius fracture. Four studies including three RCTs had evaluated the effect of bisphosphonate on distal radius fracture. In a prospective single-center double-blind RCT, a total of 37 patients with low BMD and acute distal forearm fracture were randomized to either receive daily alendronate (10 mg) therapy within 2–4 weeks of surgery or placebo and followed up for 1 year.[29] There was no difference in fracture healing time and functional outcome (as assessed by the Lidstrom scoring system) between the two groups. In another RCT, which evaluated the effect of timing of initiation of alendronate on the healing of distal radius fracture in osteoporotic patients, 50 women were randomized into group 1 (alendronate initiated at 2 weeks) and group 2 (alendronate initiated at 3 months).[30] There was no significant difference in time needed for radiological union between the two groups (group 1: 6.7 ± 1.5 weeks; group 2: 6.8 ± 1.6 weeks; $p = 0.65$). The number of patients in whom fracture got united by 6 weeks follow-up, were also similar between the two groups ($p = 0.81$). There was no difference in functional outcome as assessed by DASH (Disabilities of the Arm, Shoulder and Hand) score ($p = 0.61$). Small sample size, short follow-up of 6 months, and inclusion of only female patients were the drawbacks of this study. In a multicenter placebo-controlled RCT (Fracture and Bisphosphonate trial), patients with distal radius fracture were randomized to weekly alendronate (70 mg/week) or placebo.[31] The medication was started within 2 weeks of surgery and continued for 26 weeks. A total of 421 patients (215 in alendronate and 206 in placebo) were included in the study. There was no difference in the proportion of the patients with healed fracture at 4 weeks (primary outcome) of follow-up (OR: 0.78, CI 0.48–1.26, $p = 0.31$). Similarly, there was no difference in fracture healing at other time points of 2, 6, and 8 weeks of follow-up and all the fractures in both groups healed by 24 weeks of follow-up. No difference in fracture healing was evident in the time-to-event analysis also. There was no difference in clinical outcome between the two groups, as evaluated by DASH and pain scores. Grip strength and range of movement at the wrist were also similar at 26 weeks of follow-up. In a non-randomized prospective clinical trial from Japan,[32] 80 patients with acute fragility fracture of distal radius were allocated to two groups depending upon odd or even day of admission method. Weekly oral alendronate (35 mg/week) therapy was started within 4 days of surgery in group 1 (40 patients) and after 4 months of surgery in group 2 (40 patients). In this study, three blinded individual assessors (two orthopedic surgeons and one radiologist) evaluated the radiological healing of fracture based on five parameters, namely, initial early trabecular healing, complete early trabecular healing, initial cortical bridging, complete cortical bridging, and initial remodeling. Overall, there was no significant difference in the healing time between the two groups. However, one assessor reported a mean delay of 6 days in initial early trabecular healing time (1.3 months *versus* 1.1 months, $p = 0.038$) and another reported a mean delay of 12 days in complete cortical bridging (3.1 months *versus* 2.7 months, $p = 0.021$) in the alendronate group. The authors reported that these two findings were not considered significant as the differences were of less than 15 days. There was no significant difference in functional outcomes as assessed by grip strength, wrist range of movement, and QuickDASH (Quick Disabilities of the Arm, Shoulder, and Hand) questionnaire score at 6 months follow-up. Chance of selection bias due to non-randomized allocation and inability to assess complete remodeling time of hard callus due to short follow-up period, were the important limitations of this study. To summarize, the evidence from these above-mentioned RCTs did not show any delay of distal radius fracture healing associated with early initiation of bisphosphonate therapy.

Effect on proximal humerus fracture. A cohort of 82 osteoporotic patients of proximal humerus fracture was retrospectively divided into two groups according to the timing of initiation of weekly oral alendronate (70 mg/week).[33] In the patients of group 1, bisphosphonate was started within 2 weeks of surgery, whereas for those in group 2, it was started at 3 months after surgery. The patients were followed up for 1 year after surgery. The authors did not find any difference in time taken for radiological union among the two groups (6.3 weeks *versus* 6.6 weeks, $p = 0.57$). The number of patients with evidence of fracture healing within 6 weeks of surgery was also similar between the two groups (82% *versus* 77%, $p = 0.16$). Clinical outcome after 1 year of surgery as assessed by the American Shoulder and Elbow Surgeons (AESS) scoring system ($p = 0.61$), Constant score ($p = 0.63$), and range of movement of the shoulder ($p = 0.89$) were also similar between the two groups. Small sample size, short follow-up, and lack of measurement of BMD were the limitations of the study.

Effect on leg fracture. Two RCTs had evaluated the effect of bisphosphonate on the healing of leg fractures. In a double-blinded single-center RCT, 38 patients with lower leg fractures were randomized to receive either alendronate (10 mg daily) or placebo within 2 weeks of the surgery.[34] There were only two reported cases of non-union, one from each of the groups during the follow-up. In the study by Harding *et al.*,[35] 46 patients with knee osteoarthritis, who underwent high tibial osteotomies were randomized to receive either 4 mg IV ZA ($n = 25$) or placebo ($n = 21$) after 4 weeks of surgery. There was no difference in the healing time between ZA (77 days; 95% CI: 75–80) or placebo (77 days; 95% CI: 74–81) arms. The mean difference (MD) in healing time between the two groups was 0.2 (CI: −4.4 to 4.8) days. All the osteotomies in both groups were healed by 16 weeks of follow-up. After 18 months of follow-up, all the patients retained the surgical corrections. Thus, overall, there was no significant evidence of any detrimental effect of initiation of bisphosphonate therapy following leg surgeries.

Effect on spinal surgeries. The effect of early bisphosphonate therapy on the healing process following spinal surgeries was also studied in the literature. In the RCT by Nagahama *et al.*,[36] 36 patients with osteoporosis who underwent single-level posterior lumbar interbody fusion (PLIF) surgery, were randomized to either alendronate (35 mg/week) or control groups (alphacalcidiol). The study drugs were started within 1 week of surgery for a duration of 12 months. Patients in the alendronate group ($n = 19$) had shown a significantly higher spinal fusion rate in comparison with the control group (95% *versus* 65%, $p = 0.02$). However, there was no significant difference in the Oswestry Disability Index (ODI) score between the two groups at 12 months of follow-up. In a placebo-controlled double-blind RCT,[37] 82 patients with transforaminal lumbar interbody fusion (TLIF) surgery were randomized to receive either 5 mg IV ZA (41 patients) or placebo (41 patients) 3 days after the surgery. Patients with a previous bisphosphonate or teriparatide exposure were also included in this study if there was sufficient washout time. There were no significant differences in number of spinal levels showing non-union at either 6 (27.9% *versus* 33.9%, $p = 0.60$) or 12 months after the surgery (11.5% *versus* 14.5%, $p = 0.82$). Similarly, there was no difference in the number of patients with non-union levels between the two groups (12.2% *versus* 14.6%, $p = 0.60$) at 12 months following the spinal surgery. The clinical outcome as assessed by the ODI score was similar between the two groups throughout the study period. In a retrospective study, 64 osteoporotic patients undergoing lumbar interbody fusion surgery were divided into two groups. In 32 patients, ZA (5 mg IV) was given twice (3 days and 1 year after surgery) during 2 years of study duration, whereas in the control group ($n = 32$), patients did not receive any bisphosphonate. The observed spinal fusion rate was higher in the ZA group (75%) than in the control group (56%) at 2 years of follow-up. Pedicle screw loosening (18% *versus* 45%, $p = 0.03$) and cage subsidence (28% *versus* 54%, $p = 0.03$) were significantly lower in the ZA group.[38] The ODI score was also significantly lower in the ZA group at 2 years of follow-up. In another retrospective study among patients with osteoporosis, surgical outcomes were compared in 44 patients who underwent PLIF surgery depending upon whether they received alendronate or not. There was no significant difference between the alendronate and control groups (66.7% *versus* 73.9%, $p = 0.599$).[39] In a meta-analysis, bisphosphonate was shown to promote fusion in the early postoperative period (6 months), but the fusion rate was not statistically different from the control group at 12 months

after spinal surgery.[40] To summarize, the available studies in the literature showed either improved[36,38] or comparable[37,39] surgical outcomes with early bisphosphonate therapy. Thus, early bisphosphonate therapy is unlikely to hinder the healing process of spinal fusion surgeries.

Overall effect on fracture. In a meta-analysis that evaluated the effect of early initiation of bisphosphonate therapy following surgery on fracture healing, 10 RCTs with 2888 patients were included.[41] Among the bisphosphonates, alendronate (four studies), ZA (three studies), risedronate (two studies), and etidronate (one study) were used. Healing time was compared between the early initiation group as defined by the use of bisphosphonate within 3 months of surgery and the comparator group. This comparator group comprised either the patients without any drug therapy or those with late initiation of bisphosphonate therapy or a placebo after 3 months of surgery. In the included studies, either the patients did not have any prior bisphosphonate exposure or underwent a significant washout period. Among the included studies, the sites of surgery were hip (six studies), followed by distal radius (two studies), knee, and spine (one each). The pooled analysis did not show any significant difference in radiological healing time between the early bisphosphonate group and the comparator group [four studies; MD: 0.47, 95% CI: −2.75 to 3.69; $p = 0.34$]. Similarly, there was no significant difference in the risk of delayed or non-union of fracture among the two groups (four studies; OR: 0.98, 95% CI: 0.64–1.50; $p = 0.30$). The small sample size of included studies, pooling three types of control population together in comparator group and lack of fracture site-wise subgroup analysis were the major limitations of this meta-analysis.

In another meta-analysis by Xue *et al.*,[40] eight RCTs involving 2508 patients were included. In this meta-analysis, studies involving early bisphosphonate therapy were compared with control studies involving either placebo or no therapy (control studies) and with those involving late bisphosphonate therapy (timing studies). The authors did not find any difference in the fracture healing between bisphosphonate and the control group both in short-term (<3 months) [two studies; relative risk (RR) 1.40, 95% CI: 0.36–5.49; $p = 0.63$] as well as long-term (>12 months) [four studies; RR: 1.00, 95% CI: 0.98–1.02; $p = 0.90$] follow-up. Pooled analysis of the timing studies also did not show any significant difference in fracture healing time between early (<1 month) and late (>1 month) bisphosphonate initiation following surgery [two studies; MD: −0.20, 95% CI: −1.03 to 0.63; $p = 0.64$]. Gao *et al.*[42] also did not find any significant difference in fracture healing time between the bisphosphonate and the pooled comparator group [five studies; SMD: 0.17, 95% CI: −0.09 to 0.42; $p = 0.21$]. However, in their meta-analysis, studies with prior bisphosphonate use were analyzed together along with the studies where it had been initiated after surgery. Overall, the evidence from these studies suggests that the early (<4 weeks) initiation of bisphosphonate following surgery is not associated with any significant prolongation of fracture healing time or any increase in non-union rate. There was no evidence of any detrimental effect on functional outcomes with early bisphosphonate use. The summary of the findings of these RCTs is given in Table 1.

Effect on BMD, subsequent fracture and mortality. Moreover, early initiation of ZA has its own additional advantages in improving overall bone health, decreasing the risk of subsequent fracture, and reducing the mortality rate. In a retrospective cohort study from Taiwan,[43] patients were divided into early initiation of bisphosphonates (EIBP) and late initiation of bisphosphonates (LIBP) groups, depending upon the timing of initiation of weekly alendronate (70 mg) therapy. In the EIBP group, alendronate was started within 3 months of the first fragility fracture, while on the contrary, it was started after 3 months in the LIBP group. The incidence of second fragility fracture (32.44% *versus* 19.08%, $p = 0.0005$) and surgery for second fragility fracture (18.70% *versus* 9.16%, $p = 0.0021$) were significantly higher in the LIBP group. In a placebo-controlled study that included 114 patients with intertrochanteric fracture, patients were administered either 5 mg of IV ZA or placebo at 2 weeks following surgery.[44] The mortality rate was found to be significantly less in the ZA arm than the placebo arm (14.3% *versus* 34.5%, $p = 0.012$). In the meta-analysis by Gao *et al.*,[42] BMD was found to be significantly higher in the bisphosphonate arm than the comparator arm [standardized mean difference (SMD): 2.31, 95% CI: 0.38–2.39; $p = 0.007$). Eriksen *et al.*[45] also reported a significant reduction in the incidence of subsequent fractures as well as a reduction in the mortality

Table 1. Summary of the randomized control trials evaluating the effect of early initiation of bisphosphonates.

No	Author	BP used	Study group *versus* comparator	Fracture	Follow-up	Outcome on fracture healing
1	Colón-Emeric *et al.*[23]	Zoledronic Acid 5 mg IV	ZA group *versus* placebo Sub group analysis: 1. Within 2 weeks, 2. >2–4 weeks, 3. >4–6 weeks, 4. >6 weeks	Hip (low-trauma)	1 year	1. No association between timing of ZA infusion following surgery and delay in fracture healing ($p = 0.44$)
2	Kim *et al.*[24]	Alendronate 35 mg weekly	3 groups: A. After 1 week B. after 1 month C. After 3 months of surgery	Intertrochanteric	1 year	1. No difference in radiological healing time: A (10.7 ± 4.4), B: (12.9 ± 6.2), and C: (12.3 ± 7.1) weeks ($p = 0.42$)
3	Li *et al.*[25]	Zoledronic Acid 5 mg IV	ZA (day 3 post surgery) *versus* Control	Intertrochanteric	1 year	1. Faster healing time in ZA (13 ± 3.2 weeks) *versus* control (15 ± 4.6 weeks) ($p = 0.02$)
4	Sargin *et al.*[26]	Zoledronic Acid 5 mg IV	Three groups: 1. ZA within 1 week + PFN 2. ZA within 1 month + PFN 3. ZA within 1 week + Hemiarthroplasty	Intertrochanteric	1 year	1. No difference in radiological healing between groups 1 and 2
5	Jalan *et al.*[27]	Zoledronic Acid 5 mg IV	Group 1a: within 1 week Group 1b: at 6 weeks Group 2: control	Intertrochanteric	1 year	1. No difference in fracture union time: 1a (13.7 ± 2.8), 1b (13.7 ± 3.5) and 2 (14.2 ± 2.8) weeks ($p = 0.69$)
6	van der Poest Clement *et al.*[29]	Alendronate 10 mg daily	Alendronate (within 2–4 weeks) *versus* control	Distal forearm	1 year	No significant difference in healing time between two groups
7	Gong *et al.*[30]	Alendronate 70 mg weekly	Group 1: from 2 weeks after surgery; Group 2: from 3 months after surgery	Distal radius	24 weeks	1. No difference in time to radiological fracture healing ($p = 0.65$) 2. No difference in number of patients with fracture healing at 6 weeks follow-up ($p = 0.814$)
8	Duckworth *et al.*[31]	Alendronate 70 mg weekly	Alendronate (within 2 weeks) *versus* placebo	Distal radius	26 weeks	1. Proportion of fracture united at 4 weeks was similar (OR: 0.78, CI: 0.48–1.26, $p = 0.31$) and also at 2 weeks, 6 weeks, and 8 weeks. 2. All the fractures were healed in both groups healed at 24 weeks
9	van der Poest Clement *et al.*[34]	Alendronate 10 mg daily	Alendronate (within 2 weeks) *versus* placebo	Leg and ankle	1 year	1. 1 non-union each in both groups

(Continued)

Table 1. (Continued)

No	Author	BP used	Study group *versus* comparator	Fracture	Follow-up	Outcome on fracture healing
10	Harding *et al.*[35]	Zoledronic Acid 4 mg IV	ZA (4 weeks) *versus* placebo	High tibial osteotomies	1.5 years	1. No difference in healing time of osteotomies between the two groups (77 days; 95% CI 75–80 *versus* 77 days; 95% CI: 74–81). 2. All the osteotomies in both groups were healed by 16 weeks' time.
11	Nagahama *et al.*[36]	Alendronate 35 mg weekly	Alendronate (within 1 week) *versus* control group (alpha-calcidiol)	Posterior lumbar interbody fusion surgery	1 year	1. Higher spinal fusion rate in the alendronate group than the control group (95% *versus* 65%, p = 0.02)
12	Li *et al.*[37]	Zoledronic Acid 5 mg IV	ZA group (day 3 after surgery) *versus* placebo	Transforaminal lumbar interbody fusion surgery	1 year	1. No significant differences in number of spinal levels showing non-union at 6 months (27.9% *versus* 33.9%, *p* = 0.60) or 12 months (11.5% *versus* 14.5%, *p* = 0.82) 2. No difference in number of patients with non-union levels between two groups (12.2% *versus* 14.6%, *p* = 0.60) at 12 months.

BP, Bisphosphonate; CI, confidence interval; IV, intravenous; OR, odds ratio; PFN, proximal femoral nail; ZA, zoledronic acid.

rate in patients who received ZA at 2 weeks or later following low-trauma hip fracture in comparison with placebo.

Denosumab. In phase III FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months),[46] denosumab was shown to reduce the risk of vertebral, nonvertebral, and hip fractures over 3 years in postmenopausal women with osteoporosis. In this trial, as scheduled denosumab administration was not adjusted following a fracture, this provided an opportunity to evaluate the effect of denosumab on the fracture healing. In a preplanned analysis of the FREEDOM trial, Adami *et al.*[47] studied the effect of denosumab on fracture healing in patients presenting with nonvertebral fracture. A total of 667 subjects (303 in the denosumab group and 364 in the placebo group) experienced 851 nonvertebral fractures (386 in the denosumab group and 465 in the placebo group). Seven patients experienced delayed healing (two in the denosumab group and five in the placebo group). In this study, delayed healing or non-union was not observed in any subject who received denosumab within 6 weeks preceding or following the fracture. Fracture healing seemed to be unaffected in patients treated with denosumab, even when administered within a day of the fracture.

Anabolic drugs

PTH and analogs. In this section, studies evaluating effect of PTH and its analogs on fracture healing are reviewed (Table 2). PTH (1-34) (teriparatide) and a PTHrP analog (abaloparatide) are the two licensed peptides that are approved currently. PTH (1-84) was used for several years in Europe but is not currently available for this indication.

Effect on hip fracture. In a retrospective observational study by Huang *et al.*,[54] 189 patients who underwent surgical interventions postosteoporotic

Table 2. Summary of the randomized control trials evaluating the effect of early initiation of parathyroid hormone.

No	Author	Agent used	Study group *versus* comparator	Fracture site	Time of initiation	Outcome on fracture healing
1	Rana *et al.*[48]	PTH (1-34)	Group A: control Group B: Teriparatide 20 mcg	Intertrochanteric	1st postoperative day	Time to fracture union reduced by about 2 weeks in the teriparatide group
2	Chesser *et al.*[49]	PTH (1-34)	Teriparatide *versus* control	Trochanteric	Within 10 days of surgery	No difference in union rate
3	Bhandari *et al.*[50]	PTH (1-34)	Teriparatide 20 mcg *versus* placebo	Femoral neck	Within 14 days	Prematurely stopped due to very slow patient accrual, but no difference radiological union rate. Teriparatide did not decrease the risk of revision surgery, improve radiographic signs of fracture healing, or decrease pain compared with the placebo
4	Aspenberg *et al.*[51]	PTH (1-34)	3 groups: 1. Placebo 2. Teriparatide 20 mcg 3. Teriparatide 40 mcg	Distal radial	Within 10 days	Significantly shorter radiographic healing time in teriparatide 20 mcg group ($p = 0.006$) *versus* placebo
5	Almirol *et al.*[52]	PTH (1-34)	Teriparatide 20 mcg *versus* placebo	Lower-extremities (stress fractures)		Bone biomarkers P1NP and OC increased more in the teriparatide group (both $p \leqslant 0.01$). Teriparatide may help hasten fracture healing.
6	Peichl *et al.*[53]	PTH (1-84) 100 mcg/day	PTH (1-84) *versus* control	Pubic	Within 2 days	Significantly reduced fracture healing time in treatment group [7.8 weeks *versus* 12.6 weeks($p < 0.001$)]

OC, osteocalcin; P1NP, N-terminal propeptide of type I procollagen; PTH, parathormone.

intertrochanteric fractures were enrolled and divided into three groups. Group 1 patients ($n = 83$) received only calcium and vitamin D postoperatively, group 2 ($n = 47$) received teriparatide along with calcium and vitamin D, and group 3 ($n = 59$) comprised patients who were already on alendronate prior to fracture and received teriparatide post fracture. Those patients who received PTH (teriparatide) were started on 20 mcg/day dose subcutaneously beginning on the day of surgery. Time to union was found to be significantly shorter in the teriparatide treated groups [mean, 13.6, 12.3, and 10.6 weeks, respectively ($p = 0.002$)]. Health-related quality of life score SF-12 PCS and pain scores were significantly better in teriparatide-treated groups at 3 and 6 months. Thus, in this study, teriparatide proved to play an effective adjunctive role in the treatment of osteoporotic intertrochanteric fractures. In yet another retrospective study, Huang *et al.*[55] analyzed the outcomes of unstable pertrochanteric fractures in patients who underwent dynamic hip screw fixation. Teriparatide was administered subcutaneously at the dose of 20 mcg/day from the day of surgery. Fracture healing time was significantly shortened in the teriparatide treated group ($n = 29$) than in the control group ($n = 44$). The mean overall mobility scores were significantly

better in the teriparatide group at 3 and 6 months ($p < 0.001$ and $p < 0.001$, respectively) but not at 12 months or the last follow-up. The pain scores were also significantly better in the teriparatide treated group at 3 and 6 months but not at 12 months or the last follow-up. In another prospective randomized controlled open-label study, Rana *et al.*[48] evaluated the effect of teriparatide in surgically fixed osteoporotic intertrochanteric femur fractures. Patients were randomized to receive only calcium and vitamin D supplementation (group A) or teriparatide at a dose of 20 mcg/day (group B) beginning on the first post-operative day. Thirty patients were included in the final analysis. All the patients achieved fracture union by the end of 20 weeks. However, time to fracture union was reduced by about 2 weeks in the teriparatide group, along with better functional outcome and improvement in BMD.

Kim *et al.*[56] retrospectively assessed the effect of short-term daily teriparatide in patients who underwent closed reduction and internal fixation with proximal femoral nail (PFN) for unstable intertrochanteric fractures. Group 1 ($n = 60$) was treated with PFN alone and group 2 ($n = 52$) additionally received a daily subcutaneous injection of teriparatide 20 mcg postoperatively for 2 months. Teriparatide significantly increased Harris hip score (HHS) ($p = 0.02$) and decreased VAS pain scores ($p = 0.008$). The mean time to fracture healing was 14.8 weeks in group 1 and 12.1 weeks in group 2 ($p = 0.002$). Among other RCTs, one was a pilot study among 29 trochanteric hip fracture patients which found no difference in union rate.[49] It has a major limitation in the form of small groups, which might have precluded proper assessment of the effect of PTH. Bhandari *et al.*[50] in a randomized placebo-controlled trial evaluated the effect of teriparatide 20 mcg/day for 6 months *versus* placebo on femoral neck fracture healing at 24 months. A total of 159 patients were randomized: teriparatide ($n = 78$) and placebo ($n = 81$). Within 14 days after internal fixation, patients were randomized in a 1:1 ratio. In this study, teriparatide did not decrease the risk of revision surgery, improve radiographic signs of fracture healing, or decrease pain when compared with placebo. This study was pooled analysis of two RCTs with a planned enrolment of 1220 patients per trial. As the final number of patients analyzed was much less than planned, the small sample size must have limited the ability to detect a difference in the revision surgery.

In a meta-analysis of two RCTs and four retrospective studies comprising 607 patients, Han *et al.*[57] assessed the role of teriparatide in improving hip fracture healing. Compared with the control group ($n = 338$), teriparatide ($n = 269$) reduced the time to union [weighted mean difference (WMD) = −1:95; 95% CI: −3.23 to −0.68; $p = 0{:}003$] but did not improve the rate of fracture union at 3 months (OR: 1:46; 95% CI: 0.50–4.24; $p = 0{:}49$) or at 6 months (OR: 0:89; 95% CI: 0.44–1.81; $p = 0{:}75$). Inclusion of both RCTs as well as observational studies, heterogeneity due to different treatment protocols (daily or weekly doses of teriparatide) and dissimilar study durations (from 6 weeks to 18 months) were the major limitations of this meta-analysis.

Effect on distal radius fracture. In a prospective, randomized, double-blind, placebo-controlled, multicentre, multinational study, Aspenberg *et al.*[51] analyzed the effect of teriparatide on distal radial fractures. A total of 102 postmenopausal women with a unilateral dorsally angulated fracture of the distal radius (Colles' fracture) were randomized within 10 days of fracture to receive either 8 weeks of once-daily placebo injections or teriparatide 20 mcg or teriparatide 40 mcg. The estimated median time from fracture to radiographic healing was 9.1, 7.4, and 8.8 weeks for placebo, teriparatide 20 mcg, and teriparatide 40 mcg, respectively. When compared with placebo, the radiographic healing time was significantly shorter in the teriparatide 20 mcg group ($p = 0.006$). In a *post hoc* subgroup analysis of this trial, Aspenberg and Johansson,[58] studied the qualitative appearance of the callus 5 weeks after the fracture in 27 patients recruited at Linkoping University hospital. In this analysis, they concluded that teriparatide improves early callus formation in distal radial fractures.

Effect on lower extremity stress fracture. In a pilot placebo controlled study, Almirol *et al.*[52] evaluated short-term effects of teriparatide in premenopausal women with acute lower-extremity stress fractures. Patients were randomized to receive either 20 mcg/day of teriparatide ($n = 6$) or placebo ($n = 7$) for 8 weeks. After 8 weeks of treatment, bone biomarkers P1NP and OC increased more in the teriparatide group *versus* placebo (both $p \leqslant 0.01$), resulting in a marked anabolic window ($p \leqslant 0.05$). Thus, they concluded that, teriparatide may help hasten fracture-healing in premenopausal women with lower-extremity stress fractures.

Effect on pelvis fracture. Peichl *et al.*[53] in their prospective, randomized, controlled study evaluated the effect of PTH 1-84 on pelvic fracture healing and functional outcome. Sixty-five postmenopausal women with pelvic fractures were analyzed. Twenty-one patients were started on a 100 mcg once-daily subcutaneous injection of PTH 1-84 within 2 days of admission. The control group comprised 44 patients. Fracture healing was assessed using computed tomography scans every fourth week, until fracture healing was confirmed. Functional outcome was studied with the use of 'Timed Up and Go' test and a visual analog scale for pain. In the treatment group, the mean time to fracture healing was 7.8 weeks compared with 12.6 weeks in the control group ($p < 0.001$). At 8 weeks, the healing rate was 100% in the treatment group compared with 9.1% in the control group ($p < 0.001$). Functional outcome was significantly improved in the treatment group.

Effect on any fracture. Song *et al.*[59] studied the efficacy of intermittent parathyroid hormone treatment for stimulation of callus formation. A total of 14 patients were analyzed. Patients in group 1 received intermittent PTH after surgery while patients in group 2 were treated only with surgery. The mean time to initial callus formation, bridging callus formation and the bone union was significantly lesser for group 1 when compared with group 2. Thus, intermittent PTH administration after surgical treatment accelerated fracture healing.

Overall effect on fracture. In a meta-analysis of RCTs, Lou *et al.*[60] studied the efficacy of teriparatide in fracture healing and clinical function improvement of osteoporotic patients. Five studies with 251 patients were included. Radiological fracture healing time was significantly shorter in patients treated with teriparatide compared with those in the control group (MD:−4.54 days, 95% CI: −8.8 to −0.28). In stratified analysis, the lower limb group had a significantly shorter healing time (MD: −6.24 days, 95% CI: −7.20 to −5.29), but the upper limb group did not (MD: −1 days, 95% CI: −2.02 to 0.2). Teriparatide treatment group showed better functional outcomes than those in the control group (SMD: −1.02, 95% CI: −1.81 to −0.22). Patients with therapy duration over 4 weeks had better functional outcomes (SMD: −1.68, 95% CI: −2.07 to −1.29). The inclusion of only five studies with a small sample size and the majority of patients being female were the main limitations of this meta-analysis. In another meta-analysis of 8 RCTs including 524 patients, Hong *et al.*[61] studied the effectiveness and safety of the parathyroid hormone in fracture healing. The PTH treatment group was associated with shorter fracture healing time, lower pain scores, and better functional outcomes. However, there were no significant differences in the fracture healing rate or adverse events. Recently, in a meta-analysis of prospective RCTs, Eastman *et al.*[62] studied the effectiveness of PTH analogs in adults with acute fractures. Eleven articles comprising 1452 patients were included, 91.8% of which were women. PTH analog treatment improved functional outcomes in a range of fracture types but did not affect the fracture healing rate or reduce pain. This study did not analyze time for radiological healing.

There is no evidence that parathyroid hormone treatment impedes fracture healing or causes harm. Majority of evidence points toward the ability of teriparatide to hasten fracture healing. Moreover, studies have shown that it can be administered in any type of fracture; can be initiated at any time, even on the day of surgery, and it reduces time to fracture healing.

Parathyroid hormone-related protein (PTHrP). PTH and PTHrP both bind to the same receptor (PTH1R) with similar bioactivity in their N-terminal region. Although Abaloparatide has been shown to increase BMD at various sites in RCT,[63] data are lacking about its effect on fracture healing in humans.

Drug with anabolic and antiresorptive action

Strontium ranelate. Strontium ranelate has a dual function.[64] It activates osteoblasts and increases bone formation and inhibits osteoclasts and reduces bone absorption. Animal models have shown that strontium ranelate enhances callus strength in osteoporotic rats[65] and could promote tibial fracture healing.[66] However, an RCT conducted by Scaglione *et al.*[67] in 40 patients older than 60 years with wrist fracture, failed to show any benefit. Patients were randomly assigned into two groups: both groups (A and B) received calcium and vitamin D supplements. Group B additionally received strontium ranelate 2 g daily. In this study, strontium ranelate administered in acute phase neither improved nor accelerated fracture healing.

Comparison among different osteoporosis therapies

Among the studies available in the literature that assessed the effect of initiation of anti-osteoporosis medications on acute fracture healing, the majority have evaluated either bisphosphonate or teriparatide. Similarly, published head-to-head trials between the different anti-osteoporosis agents are also mostly restricted between these two medications. These comparative studies were done in patients with vertebral fractures,[68–72] hip fractures,[73] as well as in patients undergoing lumbar fusion surgeries.[74–76] Teriparatide has been reported to perform better than bisphosphonates in terms of radiographic healing[69,70,72] as well as functional outcomes[69,72] after acute vertebral fractures. However, in the trial by Kang *et al.*,[71] which evaluated the effect of teriparatide in patients with vertebral fracture in comparison with other anti-osteoporotic drugs (either bisphosphonate or selective estrogen receptor modulator), no significant difference has been reported. Although early use of teriparatide has been shown to improve functional outcomes in comparison with risedronate after hip fracture, no significant difference in fracture healing time has been reported.[73] In comparison with bisphosphonates, teriparatide has also been shown to improve bone fusion rate following spinal surgery (lumbar interbody fusion) in majority[74,76] but not in all of the studies.[75] A summary of the studies comparing the effect of different anti-osteoporotic agents following acute fracture is given in Table 3.

Table 3. Summary of the studies comparing different anti-osteoporotic agents following fracture.

No.	Author	Type of study	Study group	Comparator group	Timing of initiation	Fracture site/ surgery	Follow-up	Outcome on fracture healing
1	Aspenberg *et al.*[73]	RCT	Teriparatide (20 µg/day) ($n = 86$)	Risedronate (35 mg/week) ($n = 85$)	Within 2 weeks	Trochanteric hip (low-trauma)	26 weeks	1. No difference in time taken for radiographic healing ($p = 0.547$) 2. Teriparatide showed better functional mobility (TUG test) and less pain between 8 and 26 weeks 3. No difference in SF 36 score
2	Hadji *et al.*[68]	RCT	Teriparatide (20 µg/day) ($n = 86$)	Risedronate (35 mg/week) ($n = 85$)	NA (likely within weeks)	Vertebrae	18 months	1. No significant difference in reduction in back pain, quality of life or disability 2. Significantly higher increase in BMD in teriparatide arm at spine and femoral neck 3. Teriparatide group had significantly low new or worsening vertebral fracture ($p < 0.05$) at 18 months. 4. Teriparatide group had significantly less height loss (0.44 *versus* 0.70 cm, $p < 0.05$) at 18 months

(Continued)

Table 3. (Continued)

No.	Author	Type of study	Study group	Comparator group	Timing of initiation	Fracture site/ surgery	Follow-up	Outcome on fracture healing
3	Tsuchie *et al.*[69]	Retrospective study	Four groups: 1. Teriparatide daily (20 µg/day) (*n* = 10) 2. Teriparatide weekly (56.5 µg/week) (*n* = 11) 3. Risedronate (17.5 mg/week) (*n* = 13) 4. Control (*n* = 22)		NA (likely within weeks)	Vertebrae (acute)	12 weeks	1. At 12 weeks VAS significantly lower in teriparatide daily group (*versus* risedronate) and weekly group (*versus* risedronate) 2. The occurrence of I VC was significantly lower in daily teriparatide group than risedronate group 3. Vertebral collapse change at 12 weeks was significantly lower in daily teriparatide group (*versus* risedronate or control group) and in teriparatide weekly group (*versus* control) 4. At 8 and 12 weeks, kyphotic changes were significantly lower in daily teriparatide group (*versus* risedronate or control group) and at 8 weeks significantly lower in teriparatide weekly group (*versus* control)
4	Iwata *et al.*[70]	Retrospective Study	Teriparatide (20 µg/day) (*n* = 38)	Alendronate (35 mg/week) (*n* = 60)	NA (likely early)	Vertebrae	27 months (mean)	1. Decreased time to union in teriparatide arm (adjusted relative hazard ratio: 1.86, 95% CI: 1.21 – 2.83). 2. In teriparatide arm, union rate was significantly higher than the alendronate arm at 6 months (89% *versus* 68%, OR: 8.15, 95% CI: 2.02–43.33, *p* = 0.02)

(Continued)

Table 3. (Continued)

No.	Author	Type of study	Study group	Comparator group	Timing of initiation	Fracture site/ surgery	Follow-up	Outcome on fracture healing
5	Kang *et al.*[71]	Prospective non-RCT	Teriparatide (20 µg/day) ($n=14$)	Non-teriparatide group (selective estrogen receptor modulator or bisphosphonate ($n=11$)	NA (likely within weeks)	Vertebrae	> 1 year	1. No significant difference in VAS between two groups (except at week 2) 2. No significant difference in compression percentage or kyphotic angle change between two groups
6	Min *et al.*[72]	Retrospective study	Three groups: 1. Group I: control ($n=39$) 2. Group II: BP (Alendronate/ risedronate) ($n=66$) 3. Group III: teriparatide (20 µg/day) ($n=27$)		NA (likely early)	Vertebrae	NA	1. Occurrence of IVC was lower in Group III (not statistically significant) 2. Multiple regression analysis showed significantly lower incidence of IVC occurrence in Group III 3. ODI was significantly higher in Group III (36.4 ± 16.6) at final follow-up than group II (26.4 ± 6.2) or group I (28.9 ± 8.8) ($p=0.009$) 4. Improvement in the degree of numerical rating scale was better in Group III with respect to group II or group I (5.7 *versus* 3.5 *versus* 3.1, $p<0.001$)
7	Cho *et al.*[74]	Prospective Non- RCT	Teriparatide (20 µg/ day) and alendronate in 3 months cycle ($n=23$)	Alendronate (91.37 mg/week) ($n=24$)	NA (likely early)	Posterior lumbar interbody fusion	1 year	1. Faster fusion in teriparatide arm (6.0 ± 4.8 *versus* 10.4 ± 7.2 months, $p=0.006$) 2. No difference in fusion at 12 and 24 months 3. No difference in functional outcomes at 24 months (VAS, ODI)
8	Oba *et al.*[75]	RCT	Teriparatide (once weekly) ($n=50$)	Bisphosphonate (monthly/4 weekly) ($n=54$)	1 week	Multilevel lumbar interbody fusion	6 months	1. No significant difference in bone fusion score between two arms 2. No significant difference in the rate of either screw loosening or cage subsidence between two groups

Table 3. (Continued)

No.	Author	Type of study	Study group	Comparator group	Timing of initiation	Fracture site/ surgery	Follow-up	Outcome on fracture healing
9	Wang *et al.*[76]	Retrospective cohort	Teriparatide (20 µg/day) (*n* = 29)	IV zoledronate 5 mg once (n = 38)	Teriparatide at day 1 and zoledronate Acid at day 3	Transforaminal lumbar interbody fusion	6 months	1. BMD of the spine was significantly higher in teriparatide arm than zoledronate arm 2. Significantly higher fusion rate at 12 months in teriparatide arm (86% *versus* 70%) 3. No significant difference in VAS and ODI score between two groups

BMD, bone mineral density; BP, bisphosphonate; CI, confidence interval; IVC, intravertebral cleft; NA, not available; ODI, Oswestry disability index; OR, odds ratio; RCT, randomized control trial; SF36, short form 36; TUG, timed up-and-go test; VAS, visual analog scale.

Conclusion

The period following an osteoporotic fragility fracture gives a window of opportunity to start osteoporosis medication. Bisphosphonates are safe to initiate following an acute fracture as no significant delay in fracture healing has been reported in most of the studies. Initiation of bisphosphonate has the additional advantages of prevention of future fracture as well as improvement in associated mortality and morbidity. Teriparatide due to its anabolic properties can hasten fracture healing and can be initiated early following fracture. As per the studies reviewed in the literature, both bisphosphonate and teriparatide can be safely initiated by 2 weeks following the incidence of any fracture. Studies related to the timing of initiation of other osteoporosis medications are sparse in the literature and warrants future research.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Rajan Palui: Conceptualization; Data curation; Validation; Writing – original draft.

Harsh Durgia: Methodology; Resources; Writing – original draft.

Jayaprakash Sahoo: Conceptualization; Supervision; Validation; Writing – review & editing.

Dukhabandhu Naik: Validation; Writing – review & editing.

Sadishkumar Kamalanathan: Conceptualization; Project administration; Supervision; Validation; Writing – review & editing.

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