Osteoporosis treatment in patients undergoing spinal fusion: a systematic review and meta-analysis

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OBJECTIVE Bisphosphonates and teriparatide are the most common therapies used in the treatment of osteoporosis. Their impact on fusion rates in osteoporotic patients following spinal fusion has yet to be concretely defined, with previous systematic reviews focusing heavily on bisphosphonates and lacking clinical insight on the utility of teriparatide. Herein the authors present an updated meta-analysis of the utility of both bisphosphonates and teriparatide in improving spinal fusion outcomes in osteoporotic patients.

METHODS After a comprehensive search of the English-language literature in the PubMed and Embase databases, 11 clinical studies were included in the final qualitative and quantitative analyses. Of these studies, 9 investigated bisphosphonates, 7 investigated teriparatide, and 1 investigated a combination of teriparatide and denosumab. Odds ratios and 95% confidence intervals were calculated where appropriate.

RESULTS A meta-analysis of the postoperative use of bisphosphonate demonstrated better odds of successful fusion as compared to that in controls during short-term monitoring (OR 3.33, 95% CI 1.72–6.42, $p = 0.0003$) but not long-term monitoring ($p > 0.05$). Bisphosphonate use was also shown to significantly reduce the likelihood of postoperative vertebral compression fracture (VCF; OR 0.07, 95% CI 0.01–0.59, $p = 0.01$) and significantly reduce Oswestry Disability Index scores (mean difference [MD] = -2.19 , 95% CI -2.94 to -1.44 , $p < 0.00001$) and visual analog scale pain scores (MD = -0.58 , 95% CI -0.79 to -0.38 , $p < 0.00001$). Teriparatide was found to significantly increase fusion rates at long-term postoperative periods as compared to rates after bisphosphonate therapy, with patients who received postoperative teriparatide therapy 2.05 times more likely to experience successful fusion (OR 2.05, 95% CI 1.17–3.59, $p = 0.01$).

CONCLUSIONS The authors demonstrate the benefits of bisphosphonate and teriparatide therapy independently in accelerating fusion during the first 6 months after spinal fusion surgery in osteoporotic patients. In addition, they show that teriparatide may have superior benefits in spinal fusion during long-term monitoring as compared to those with bisphosphonates. Bisphosphonates may be better suited in preventing VCFs postoperatively in addition to minimizing postoperative disability and pain.

<https://thejns.org/doi/abs/10.3171/2021.3.FOCUS2175>

KEYWORDS osteoporosis; spinal fusion; bisphosphonate; teriparatide; fracture; meta-analysis

OSTEOPOROSIS is a common metabolic bone disease, affecting about 10.2 million US adults aged 50 years and older.¹ Patients with osteoporosis have an increased risk of vertebral compression fractures (VCFs), occurring in approximately 550,000 osteoporotic patients each year.^{1–3} Osteoporosis occurs because of an imbalance between osteoclast activity, which is responsible for bone resorption, and osteoblast activity, leading to decreased bone mass.² Osteoporosis is diagnosed when a World Health Organization T-score of -2.5 or lower is detected on a dual-energy x-ray absorptiometry (DEXA)

scan.⁴ Furthermore, in patients requiring spinal fusion, osteoporosis may impair fusion because fusion is dependent on appropriate bone formation and remodeling.³ In addition to having lower fusion rates, patients are at an increased risk of cage subsidence, screw loosening, iatrogenic fractures, and proximal junctional kyphosis.⁵

Osteoporosis treatments may increase fusion rates in patients with lower bone mineral density (BMD) following spinal fusion. Among these therapies, bisphosphonates constitute the broadest and oldest class of drugs, suppressing bone resorption by binding to hydroxyapatite and pre-

ABBREVIATIONS BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry; MD = mean difference; ODI = Oswestry Disability Index; P1NP = amino-terminal propeptide of type 1 procollagen; RANKL = receptor activator of nuclear factor κ B ligand; VAS = visual analog scale; VCF = vertebral compression fracture.

SUBMITTED February 1, 2021. **ACCEPTED** March 19, 2021.

INCLUDE WHEN CITING DOI: 10.3171/2021.3.FOCUS2175.

venting its enzymatic cleavage.⁶ Anabolic agents are more modern medications, with teriparatide being the most widely studied. In contrast to bisphosphonates, teriparatide exerts its action by directly stimulating surface receptors in osteoblasts to amplify bone formation.⁷ The use of these treatments in osteoporotic patients has prompted investigation into their utility in the perioperative management of patients undergoing spinal fusion, with multiple animal studies having investigated both classes of drugs.^{5,8–12}

Though clinical evidence supporting the use of osteoporosis therapies is expanding, there are few comprehensive meta-analyses investigating both bisphosphonates and teriparatide. While previous meta-analyses evaluating the impact of these agents on spinal fusion exist, these studies have focused heavily on the role of bisphosphonates.^{13–15} Furthermore, there have been very few recent systematic reviews detailing the impact of teriparatide on spinal fusion rates and none with meta-analyses of the available data.¹⁶ We present a comprehensive systematic review and meta-analysis of osteoporosis therapies and their impact on spinal fusion rates and offer novel findings on the utility of teriparatide in the postoperative treatment of osteoporotic patients who have undergone spinal fusion.

Methods

Inclusion and Exclusion Criteria

Studies evaluating clinical and radiological outcomes of spinal fusion in humans with osteoporosis were included in this review. The exclusion criteria were as follows: 1) studies with nonhuman cohorts; 2) studies that did not incorporate pharmacological management; 3) studies without a comparison or control group; 4) studies that did not evaluate spinal fusion outcomes; 5) studies that did not include a measurement of the fusion rate or a biomechanical, histological, radiographic, or microstructural assessment of fusion quality; 6) studies without a statistical analysis; and 7) case reports.

Literature Search and Selection

We performed a systematic search of the English-language literature dating from July 1990 to October 5, 2020, in the PubMed and Embase databases. The following medical subject heading (MeSH) terms and free text words were used: “spinal fusion” or “arthrodesis” or “spine” or “osteoporosis” or “osteoporotic.” A total of 247 published abstracts or papers were identified. As displayed in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart (Fig. 1), after applying the inclusion and exclusion criteria, a total of 11 papers were included in the qualitative analysis and 9 in the quantitative analysis. Selection and data extraction of the studies were independently performed by two authors (V.G. and A.D.).

Data Analysis

The pooled data analysis was performed with Review Manager 5.4 (RevMan, Cochrane). Odds ratios and 95% confidence intervals were calculated using the Mantel-Haenszel test, and forest plots were generated for each comparison. Random-effects dichotomous models were

developed to assess the overall effect of each drug in control and treatment groups. Our primary outcome of interest was fusion rate. Other secondary outcomes included VCF, postoperative screw loosening, postoperative BMD, postoperative Oswestry Disability Index (ODI), and postoperative visual analog scale (VAS) pain score. Risk of bias was assessed using the Cochrane risk-of-bias tool in order to give further insight into the conclusions made by us and our own subsequent meta-analyses.

Results

Study Selection and Characteristics

Eleven articles met the inclusion criteria from an initial pool of 247 articles.^{2,5,6,8–12,21,31,47} All studies had a controlled design and evaluated fusion mass radiographically, surgically, histologically, or a combination thereof. Nine studies were included in the quantitative analysis.^{2,5,6,10–12,21,31,47} Key differences are summarized in Table 1. Nine studies investigated bisphosphonates, 7 reviewed teriparatide, and 1 studied denosumab, a monoclonal receptor activator of nuclear factor κ B ligand (RANKL) antibody. Among the bisphosphonate studies, 5 used a negative control arm and the other 4 compared outcomes to a teriparatide treatment arm. Among the teriparatide studies, 2 had a negative control arm, 1 compared outcomes to a denosumab treatment arm, and the others compared outcomes to a bisphosphonate treatment arm. All studies evaluated fusion outcomes using CT and/or radiographs with dynamic views. All studies administered their interventions solely postoperatively except the study performed by Ide et al. (1 month preoperatively and 12 months postoperatively) and the studies performed by Ohtori et al. (treated 2 months prior in Ohtori et al., 2012 and 2013, and 3 months prior in Ohtori et al., 2015).^{8–11} The studies by Ohtori et al. also treated patients for 8 months, 10 months, and up to 10 months postoperatively in 2012, 2013, and 2015, respectively.^{9–11}

Characteristics of the intervention and control arms of the studies included in the quantitative analysis are summarized in Table 2. The numbers of intention-to-treat patients in the bisphosphonate, teriparatide, and control arms are also presented in Table 2. A risk-of-bias summary is presented in Fig. 2.

Fusion Rates

Fusion rates in most studies were reported as the number of fused index levels per total index levels assessed. Among the bisphosphonate versus negative control studies, 3 reported fusion rates at 6 months and 4 reported rates at 12 months postoperatively. Of the 102 levels that underwent fusion surgery in the bisphosphonate treatment arm and were evaluated for successful fusion at 6 months, 83 (81.4%) met grade A or B fusion criteria based on the Bridwell system¹⁷ for either bilateral or unilateral bridging bone formation, respectively. In the control arm at 6 months, 65 (59.6%) of 109 levels met fusion criteria. At 12 months, 105 (85.4%) of 123 levels in the bisphosphonate treatment arm and 110 (83.3%) of 132 levels in the control arm met fusion criteria. A Cochran-Mantel-Haenszel test demonstrated higher odds of successful fusion among

FIG. 1. Study flow diagram. Data added to the PRISMA template [from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097] under the terms of the Creative Commons Attribution License.

patients taking bisphosphonates versus unmedicated controls at 6 months postoperatively (OR 3.33, 95% CI 1.72–6.42, $p = 0.0003$) but not at 12 months postoperatively (OR 1.14, 95% CI 0.47–2.79, $p = 0.77$; Fig. 3A and B). This suggests that bisphosphonate therapy might increase the rate of fusion only during the initial postoperative period (≤ 6 months) and not the long term.

Among the bisphosphonate versus teriparatide studies, 3 reported outcomes at 12 months and only 1 reported outcomes at 6 months. At 12 months, 122 (83.0%) of 147 levels in the teriparatide treatment arm and 103 (70.5%) of 146 levels in the bisphosphonate treatment arm met fusion criteria. When pooled, patients in the teriparatide treatment arm had significantly higher odds of success-

ful fusion relative to bisphosphonate patients at 12 months (OR 2.05, 95% CI 1.17–3.59, $p = 0.01$; Fig. 3C). Although meta-analysis was not possible for outcomes at 6 months, Cho et al. demonstrated higher fusion rates in teriparatide patients relative to those in bisphosphonate patients at 6 months.⁵ In a prospective study of 47 patients, they observed that 21 (77.8%) of 27 levels in the teriparatide treatment arm and 15 (53.6%) of 28 levels in the bisphosphonate treatment arm met fusion criteria.

Among the studies investigating teriparatide, only one compared fusion rates with a negative control.⁷ Among 75 osteoporotic patients who had undergone fusion surgery, those in the teriparatide group experienced significantly higher rates of bilateral bridging bone formation

TABLE 1. Summary of studies, including primary endpoints, treatment duration, and follow-up duration

Authors & Year	Study Type	No. of Patients	Age (yrs)	T-Score	Procedure	Intervention	Control Arm	Primary Endpoint	Treatment & FU
Nagahama et al., 2011 ²	RCT	40	>18		1-level PLIF	Alendronate	Vitamin D	Fusion rate	Wkly admin for 12 mos, 12 mos FU
Chen et al., 2016 ²¹	RCT	79	>18	≤−2.5	1-level PLIF	Zoledronate	Saline	Fusion rate	Single infusion postop, 12 mos FU
Ebata et al., 2017 ⁸	RCT	74	>50		1-level PLIF or TLIF	Teriparatide	No medication	Fusion rate	Wkly admin for 6 mos, 6 mos FU
Ide et al., 2018 ⁹	RCT	16	74 ± 7		1-, 2-, or 3-level PLIF	Teriparatide & denosumab	Teriparatide	Fusion rate	Daily admin for 13 mos, 12 mos FU
Ohtori et al., 2012 ¹⁰	Pros	57	76.6 ± 6.9		1- or 2-level PLF	Teriparatide	Risedronate	Fusion rate	Daily admin for 10 mos, 12 mos FU
Ohtori et al., 2013 ¹¹	Pros	62	77.6 ± 6.0		1- or 2-level PLF	Teriparatide or risedronate	No medication	Screw loosening	Daily admin for 12 mos, 12 mos FU
Cho et al., 2017 ⁵	Pros	47	>18	<−2.5	1- or 2-level PLIF	Teriparatide	Alendronate	Fusion rate	Treated at least 12 mos, 24.7 ± 2.0 mos FU (teriparatide, daily); 29.9 ± 8.1 mos FU (alendronate, wkly)
Kim et al., 2014 ⁴⁷	Retro	44	64.7		1-level LIF	Alendronate	No medication	Fusion rate	Wkly admin until FU, mean 33.8 mos FU
Ohtori et al., 2015 ¹²	Retro	45	71.0 ± 7.0		1- or 2-level PLF	Teriparatide	Risedronate	Fusion rate	Daily teriparatide (5.5 or 13 mos) or wkly risedronate (13 mos), 18 mos FU
Ding et al., 2017 ⁶	Retro	64	>18		TLIF, unspecified levels	Zoledronate	No medication	Fusion rate	Initial infusion then another after 12 mos, 24 mos FU
Kim et al., 2018 ³¹	Retro	84	>18	<−2.5	1-, 2-, or 3-level TLIF	Teriparatide	Risedronate	Screw loosening	Daily teriparatide for 6 mos, then 6 mos risedronate or wkly risedronate for 12 mos, 12 mos FU

admin = administration; FU = follow-up; LIF = lumbar interbody fusion; PLF = posterior lumbar fusion; PLIF = posterior lumbar interbody fusion; Pros = prospective; RCT = randomized controlled trial; Retro = retrospective; TLIF = transforaminal lumbar interbody fusion; wkly = weekly. Values are expressed as the mean ± standard deviation, unless indicated otherwise.

relative to rates in controls at 6 months (69% vs 35.1%, $p = 0.013$).

VCF and Pedicle Screw Loosening

While investigators were unable to demonstrate long-term differences in the fusion rate between bisphosphonates and control, several studies reported improvement in secondary outcomes. For example, Nagahama et al. and Chen et al. reported significantly lower rates of VCF in patients receiving risedronate treatment.^{2,21} A meta-analysis of these studies on the incidence of postoperative VCF demonstrated that patients receiving bisphosphonates were less likely to experience VCF than were patients who did not undergo bisphosphonate therapy (OR 0.07, 95% CI 0.01–0.59, $p = 0.01$) as shown in Fig. 4C. Bisphosphonates have also been shown to limit cage subsidence and pedicle screw loosening.^{3,4}

Several studies have also measured the efficacy of medical therapy in reducing screw loosening. Most studies have reported the screw loosening incidence as the number of patients with radiographic evidence regardless of the number of fusion levels. Two studies among those investigating bisphosphonates versus a negative control and 3 studies among those investigating teriparatide ver-

sus bisphosphonate therapy reported screw loosening (Fig. 4A and B). No significant differences in the rate of screw loosening were observed between bisphosphonate therapy and negative controls (OR 0.35, 95% CI 0.03–4.23, $p = 0.41$) or between teriparatide therapy and bisphosphonate therapy (OR 0.61, 95% CI 0.27–1.37, $p = 0.23$).

BMD

BMD assessments at preoperative and postoperative time points were made in 2 studies that compared teriparatide versus bisphosphonate therapy (Fig. 5). BMD measurements in these studies were obtained from the femur neck using DEXA preoperatively and at the 1-year follow-up. No significant difference in BMD scores at the 1-year follow-up was observed between the two therapies (mean difference [MD] = 0.24, 95% CI −0.02 to 0.50, $p = 0.07$).

Clinical Outcomes: ODI and VAS

The ODI and VAS scores were commonly reported scores for measuring clinical outcomes. Meta-analysis of mean ODI scores from 3 studies comparing bisphosphonate versus a negative control demonstrated that bisphosphonate therapy is significantly associated with a lower mean ODI score than that in controls (MD = −2.19, 95%

TABLE 2. Characteristics of studies included in quantitative analyses

Authors & Year	Intervention Arm				Control Arm			
	No. of ITT Patients	No. Receiving Therapy*	Mean Preop BMD (femur neck/L1–4, T-score, or % YAM)	Mean Age (yrs)	No. of ITT Patients	No. Receiving Therapy*	Mean Preop BMD (femur neck/L1–4, T-score, or % YAM)	Mean Age (yrs)
Nagahama et al., 2011 ²	20	19	–2.6	70.2	20	17	–1.9	67.4
Chen et al., 2016 ²¹	40	33	0.485 ± 0.005/0.709 ± 0.003	65 ± 8	39	36	0.483 ± 0.005/0.698 ± 0.004	63 ± 7
Ohtori et al., 2012 ¹⁰	29	29	65 ± 5	76 ± 6.5	28	28	64 ± 6	77 ± 6.0
Ohtori et al., 2013 ¹¹	40	40	66 ± 4 (teriparatide), 64 ± 4 (risedronate)	78 ± 6.0 (teriparatide), 75 ± 5.0 (risedronate)	22	22	64 ± 6	77 ± 5.8
Cho et al., 2017 ⁵	23	23	–3.7 ± 0.6	71.0 ± 4.9	24	24	–3.5 ± 0.6	68.2 ± 8.4
Kim et al., 2014 ⁴⁷	21	21	–3.75	NA	23	23	–3.98	NA
Ohtori et al., 2015 ¹²	30	30	65.6 ± 6 (long), 63.0 ± 7.8 (short)	72 ± 7.7 (long), 69 ± 7.1 (short)	15	15	66.8 ± 8.0	71 ± 6.0
Ding et al., 2017 ⁶	30	30	NA	64.53 ± 6.86	34	34	NA	66.44 ± 6.44
Kim et al., 2018 ³¹	33	33	–3.09 ± 0.49	69.48 ± 7.76	51	51	–2.94 ± 0.39	66.75 ± 6.46

ITT = intention to treat; long = long duration; NA = not available; short = short duration; YAM = young adult mean. Values are expressed as the mean ± standard deviation, unless indicated otherwise.

CI –2.94 to –1.44, $p < 0.00001$; Fig. 6A). When teriparatide therapy was compared to bisphosphonate therapy, teriparatide patients demonstrated a nonsignificant decrease in ODI scores (MD = –1.74, 95% CI –3.74 to 0.27, $p = 0.09$; Fig. 6B). Mean VAS scores were also significantly lower in the bisphosphonate therapy group relative to those in negative controls (MD = –0.58, 95% CI –0.79 to –0.38, $p < 0.00001$; Fig. 6C). In contrast to ODI scores, VAS scores were significantly lower among patients taking teriparatide therapy than among those in the bisphosphonate arm (MD = –0.35, 95% CI –0.64 to –0.05, $p = 0.02$; Fig. 6D).

Metabolic Markers

In a retrospective study exploring fusion outcomes with zoledronate, Ding et al. measured the bone metabolic markers carboxy-terminal cross-linked telopeptide of type I collagen (β -CTX) and amino-terminal propeptide of type I procollagen (PINP) at 10 days and at 3-month intervals up to 12 months postoperatively.⁶ Both markers were significantly suppressed in the zoledronate group at all time points ($p < 0.05$), which indicates decreased bone resorption. Ebata et al., in a randomized controlled trial assessing fusion outcomes with teriparatide therapy, also measured the serum concentrations of PINP and tartrate-resistant acid phosphatase 5b (TRACP-5b) as biomarkers of bone formation and bone resorption, respectively.⁸ At 1 month postoperatively, patients in the teriparatide arm had a significantly higher serum concentration of PINP ($p < 0.012$) and a significantly lower serum concentration

of TRACP-5b at 6 months ($p < 0.001$). The authors also measured serum concentrations of alkaline phosphatase, a marker of bone formation, in their patient cohort. In the patients who received teriparatide alone, serum alkaline phosphatase concentrations were significantly higher 3 months postoperatively ($p < 0.05$).

Discussion

The increasing prevalence of osteoporosis and spine procedures has prompted interest in the utility of adjuvant medications in improving successful postoperative fusion. Currently, the two most prevalent treatment classes for decreased BMD are bisphosphonates, which inhibit the enzymatic cleavage of hydroxyapatite, and teriparatide, which directly stimulates osteoblasts to augment bone formation.^{14,15} However, the current level of evidence regarding the utility of these drug classes remains unclear, with the most recent systematic reviews on the subject lacking objective assessment of these agents' utility.^{16,18,19} In addition, short-term versus long-term effects of these medical therapies on fusion remain unclear.

Fusion Rates

Nine studies explored fusion rates in osteoporotic patients treated with medical therapy. Five of these compared bisphosphonate outcomes to negative controls,^{2,6,13,20,21} 1 compared teriparatide to negative controls,⁸ and 3 compared teriparatide to bisphosphonates.^{5,10,12}

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2016	+	+	+	+	+	+	+
Cho 2017	-	+		+	+	+	+
Ding 2017	+	+	+	-	+	+	+
Ebata 2017	+			+	-	+	+
Ide 2018	+	+		+	+	+	+
Kim 2014	+	+	+	-	+	+	+
Kim 2018	+	+	+	-	+	+	+
Nagahama 2011	+	+		+	+	+	+
Ohtori 2012	-	+		+	+	+	+
Ohtori 2013	+	+		+	+	+	+
Ohtori 2015	+	+		+	+	+	+

FIG. 2. Risk-of-bias summary for included studies. Green plus denotes low risk of bias. Red minus denotes high risk of bias. Empty cell denotes unclear risk.

The use of bisphosphonates in patients undergoing spinal fusion surgery has been a source of debate. Prior animal studies have demonstrated that bisphosphonates may negatively modulate spinal fusion by inhibiting osteoclast activity and, subsequently, bone remodeling.^{22–25} In a prospective study comparing bone fusion rates in patients taking long-term bisphosphonates (≥ 2 years) and nonusers, Kang et al. found that long-term bisphosphonate users had significant delayed union 6 months after fusion relative to that in nonusers (26% vs 42%, respectively; $p < 0.05$).²⁶ At the long-term follow-up, however, no significant differences in fusion rates were observed. The authors postulated that bisphosphonates delay bone callus maturation rather than inhibit fusion, which may explain the delay in fusion seen in the alendronate group. Conversely, in a retrospective review of patients who received a single dose of zoledronate after posterolateral fusion, Park et al. demonstrated no significant decrease in fusion mass in patients who had received zoledronate.²⁷

In all studies that explored the effects of bisphosphonate therapy on lumbar spinal fusion rates in patients with osteoporosis at 6 months or less, bisphosphonates accelerated the fusion process.^{2,6,21} At 12 months, these differences were nonsignificant. Our group analyses confirmed these observations by demonstrating higher odds of successful fusion at 6 months (OR 3.33, $p = 0.0003$) but not at 12 months (OR 1.14, $p = 0.77$).

In contrast to bisphosphonates, teriparatide administration has enhanced spinal fusion in various animal models.^{28–30} In a multicenter, prospective randomized controlled trial, Ebata et al. explored the role of once-weekly teriparatide therapy in osteoporotic women after fusion surgery.⁸ They observed that teriparatide treatment significantly enhanced rates of complete fusion at 6 months relative to rates in the control arm (69% vs 35%, $p = 0.013$). To our knowledge, long-term studies exploring fusion rates at 12 months in patients taking teriparatide versus negative controls have not been reported.

With both teriparatide and bisphosphonates having clear benefits in enhancing spinal fusion during the short-term postoperative period and a clear difference in the cost of treatment, determining differences in outcomes is important. All 3 studies that explored fusion rates between teriparatide and bisphosphonates demonstrated significantly higher rates of complete spinal fusion in the long term among the teriparatide-treated patients.^{5,10,12} This finding was confirmed in our group analysis, which demonstrated an OR of 2.05 ($p = 0.01$) for successful fusion in favor of teriparatide. Cho et al. also demonstrated a superior rate of complete fusion at 6 months in the teriparatide group (78% vs 54%).

Lastly, supplementation of teriparatide with denosumab may also improve fusion rates. In a randomized controlled trial investigating the daily use of 20 μ g of subcutaneous teriparatide therapy alone versus supplementation with 60 mg of denosumab every 6 months after fusion, Ide et al. demonstrated bone union rates of 82% and 91% at 6 and 12 months, respectively, in the combination therapy arm versus 36% and 64% in the teriparatide-alone arm.⁹ In addition, teriparatide's potent anabolic effects on bone remodeling and ability to preferentially activate osteoblasts has shown a significantly higher degree of improvement in BMD long-term (≥ 12 months) relative to that with bisphosphonates.^{5,9,31}

Bone Quality

Regarding the role of bisphosphonates in increasing bone quality, multiple studies have demonstrated the ability of bisphosphonates to prevent VCFs and screw loosening.^{32,33} In a prospective randomized controlled trial with 2027 women with osteoporosis and preexisting vertebral fractures, Black et al. demonstrated a significant reduction in subsequent VCFs among patients in the alendronate group (8%) relative to those in the control group (15%).³⁴ Our meta-analysis confirms this finding as well. Therefore, although bisphosphonates may not be the optimal therapy for augmenting fusion rates, they may have a role in preventing pathological changes, such as VCFs, and reducing postoperative pain and disability in osteoporotic patients undergoing spinal fusion.^{2,6,21} Currently,

FIG. 3. Impact of medical therapy on fusion rates at 6 (A) and 12 (B and C) months postoperatively. **A:** Patients undergoing postoperative bisphosphonate therapy were 3.33 times more likely to experience successful fusion at 6 months relative to patients who did not receive postoperative bisphosphonate treatment (OR 3.33, 95% CI 1.72–6.42, $p = 0.0003$). **B:** Patients undergoing postoperative bisphosphonate therapy did not experience any difference in fusion rates at 12 months postoperatively as compared to patients without bisphosphonate treatment (OR 1.14, 95% CI 0.47–2.79, $p = 0.77$). **C:** Patients receiving postoperative teriparatide therapy were 2.05 times more likely to experience successful fusion relative to patients who received postoperative bisphosphonate therapy (OR 2.05, 95% CI 1.17–3.59, $p = 0.01$).

animal models have demonstrated that zoledronate and teriparatide synergistically accelerate fusion mass and bone deposition.³⁵

Denosumab, a monoclonal antibody that has been used as a fracture prophylactic in postmenopausal osteoporotic females, is another potential therapy.¹⁹ It exerts its protective effects by binding to and inactivating RANKL.⁹ RANKL has been demonstrated to increase osteoclast proliferation and activity, and the reduction of estrogen in older females has been shown to increase tissue exposure to RANKL, stimulating bone resorption.³⁶ Two long-term randomized controlled clinical trials (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months [FREEDOM]) have shown that denosumab significantly reduces bone turnover markers, reduces fracture rates, and demonstrates low rates of adverse events.^{37,38} More studies investigating the impact of denosumab following spinal fusion are necessary to determine its clinical value and structural impact.

In contrast to bisphosphonates and denosumab, teriparatide has demonstrated anabolic effects by directly accelerating bone formation and fracture healing in multiple

clinical studies, including in vertebral fractures.^{39–41} Furthermore, teriparatide has been shown to be effective in short-term administrations, with fusion mass acceleration being demonstrated with treatment durations as short as 8 weeks.^{13,42,43} However, the results of our meta-analyses demonstrate that teriparatide has limited benefit in improving secondary outcomes such as postoperative pain and disability. Larger prospective trials are still needed to elucidate the true effect on clinical outcomes.

Clinical Outcomes

Clinical outcomes, as measured by ODI and VAS scores, were better in nearly all therapy groups relative to those in controls. When ODI and VAS scores were pooled, we observed that the bisphosphonate treatment was significantly associated with lower mean ODI and VAS scores relative to those in negative controls. This was in contrast to scores in the teriparatide group compared to those in a negative control group among the 3 studies included in our review.^{7,8,11} Although teriparatide is known to reduce back pain,⁴⁴ no differences in pain or ODI scores were observed

FIG. 4. Impact of medical therapy on postoperative screw loosening. **A:** No significant differences in rates of cases with screw loosening among patients receiving postoperative bisphosphonate versus controls (OR 0.35, 95% CI 0.03–4.23, $p = 0.41$). **B:** No significant differences in rates of cases with screw loosening between teriparatide and bisphosphonates was detected (OR 0.61, 95% CI 0.27–1.37, $p = 0.23$). **C:** Summary of bisphosphonates' impact on rates of postoperative VCF. Patients who received postoperative bisphosphonate therapy demonstrated significantly lower rates of postoperative VCF than the patients who did not receive postoperative bisphosphonate therapy (OR 0.07, 95% CI 0.01–0.59, $p = 0.01$).

between teriparatide and controls. Similarly, in the studies that compared teriparatide therapy with bisphosphonates as a control, no statistical difference in ODI scores between the two groups was observed.^{10,11,31} However, mean VAS scores were significantly lower in the teriparatide group.

The results of our meta-analysis suggest that postoperative teriparatide treatment may be beneficial in accelerating and promoting fusion in osteoporotic patients. Likewise, our findings suggest that teriparatide is superior to bisphosphonates in increasing fusion rates and is associated with lower postoperative VAS scores in osteoporotic patients. However, more studies comparing patients

who received postoperative teriparatide to unmedicated patients are necessary. On the basis of our analysis, we believe that teriparatide offers a superior option for rapid and complete spinal fusion relative to bisphosphonates and suggest that teriparatide be utilized immediately after surgery barring any contraindications.

Lastly, it is well known that teriparatide is costly and that some insurance companies may not cover its cost. Although a cost-benefit analysis has not been previously reported, we believe that the elevated cost of teriparatide is offset by the significantly higher rates of complete fusion associated with its use. Lower rates of fusion may expose patients to

FIG. 5. Impact of postoperative medical therapy on BMD in osteoporotic patients who underwent spinal fusion. No significant difference in mean BMD T-scores was observed between teriparatide and bisphosphonate therapy (MD = 0.24, 95% CI -0.02 to 0.50, $p = 0.07$).

FIG. 6. Impact of medical therapy on ODI and VAS scores. **A:** Patients undergoing postoperative bisphosphonate therapy had significantly lower ODI scores following bisphosphonate therapy (MD = -2.19, 95% CI -2.94 to -1.44, $p < 0.00001$). **B:** Patients undergoing postoperative teriparatide therapy did not experience significantly lower ODI scores relative to those in patients who did not undergo postoperative teriparatide therapy (MD = -1.74, 95% CI -3.74 to 0.27, $p = 0.09$). **C:** Patients undergoing postoperative bisphosphonate therapy had significantly lower VAS scores (MD = -0.58, 95% CI -0.79 to -0.38, $p < 0.00001$). **D:** Patients undergoing postoperative teriparatide therapy had significantly lower VAS scores (MD = -0.35, 95% CI -0.64 to -0.05, $p = 0.02$).

pathological fractures or revision surgery for pseudarthrosis, thus increasing long-term costs and morbidity.^{45,46} Physicians should assess which patients require a more aggressive course of biologics preoperatively (e.g., patients with more severe pathology based on a history of prior fracture and/or BMD scores) and the patient's insurance provider and prescribe treatment accordingly. Also, the assessment for teriparatide candidacy should begin prior to surgery, as the insurance approval process may be lengthy.

There may also be benefits to preoperative treatment with teriparatide, as shown by Ohtori and colleagues.¹⁰⁻¹² However, without a direct comparison of fusion rates in patients who received both pre- and postoperative therapy versus postoperative teriparatide alone, no firm conclusions can be made. However, the cost-effectiveness of teriparatide may be increased if it can be shown that fusion rates do not significantly differ between pre- and postoperative teriparatide regimens.

Study Limitations

One limitation of this work was the lack of clinical studies evaluating fusion rates in teriparatide groups relative to those in unmedicated groups. While the results of the randomized controlled trials are promising, more studies comparing teriparatide-treated patients with unmedicated patients would reinforce the utility of postoperative teriparatide use. Another limitation of this review is the variation in the fusion grading systems used in several studies. Ohtori et al. graded fusion using the Bridwell system, whereas Cho et al. used the Ito system. Another Ohtori study did not reference a specific fusion grading system.^{3,10,12} The behavior of patients undergoing long-term bisphosphonate therapy is also unknown. There are also significant variations in the dosages, treatment patterns, and study designs of the various included studies. Lastly, our risk-of-bias assessment revealed that 2 of our studies did not employ randomization, 3 did not adequately

ly blind evaluators, and 1 study disproportionately experienced dropout in its treatment arm.^{5,6,8,10,31,47} The lack of randomization in the prospective Cho and Ohtori studies is particularly concerning, as any systematic differences between their treatment and control groups could lead to erroneous conclusions.

Conclusions

Our systematic review and meta-analysis demonstrate the benefit of bisphosphonates in accelerating fusion during a short-term monitoring period of 6 months. We also show that teriparatide is likely an optimal postoperative therapy for accelerated bone healing at long-term periods following spinal fusion in osteoporotic patients because of its rapid anabolic effects. Furthermore, while bisphosphonates have been a mainstay in osteoporosis treatment, their mechanism of action and lack of efficacy in improving long-term fusion rates may restrict their role to reducing the risk of VCFs and limiting postoperative pain and disability. Similarly, denosumab may only serve a prophylactic role, but more studies are required to evaluate its utility.

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Disclosures

Dr. Wang owns stock in Innovative Surgical Devices, Medical Device Partners, Spinicity, and Kinesimetrics; is a consultant for K2M, Spineology, Stryker Spine, DePuy-Synthes Spine, and Medtronic; holds a patent with DePuy-Synthes Spine; receives royalty payments from DePuy-Synthes Spine, Children's Hospital of Los Angeles, Springer Publishing, and Quality Medical Publishing; receives grants from the Department of Defense; and is an advisory board member for Vallum. Dr. Levi receives teaching honoraria from the American Association of Neurological Surgeons and Medtronic and grant support from the Department of Defense and the National Institutes of Health (NIH-NINDS).

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