CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINES FOR PERIOPERATIVE SPINE: PREOPERATIVE OSTEOPOROSIS ASSESSMENT

Sponsored by: Congress of Neurological Surgeons (CNS) and the Section on Disorders of the Spine and Peripheral Nerves
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Abbreviations:

BMD: bone mineral density
CT: computed tomography
UE: upper extremity
HU: Hounsfield units
PJK: proximal junctional kyphosis
PJF: proximal junctional failure
PS: pedicle screw
PLIF: posterolateral lumbar interbody fusion
PLF: posterolateral spinal fusion

ABSTRACT

Background: Osteoporosis is a metabolic bone disease that commonly affects the elderly. Degenerative spinal disease that may require surgical intervention is also prevalent in this susceptible population. If undiagnosed or untreated before spine surgery, osteoporosis may result in an increased risk of postoperative adverse events. Nontreatment of osteoporosis preoperatively may be related to a poor understanding of bone physiology, a lack of standardized treatment algorithms, limited cost-effective interventions, and reluctance by spine surgeons to be the primary provider of osteoporosis management.

Objective: The objective of this evidence-based review is to develop guidelines for the preoperative assessment and treatment of osteoporosis in patients undergoing spine surgery.

Methods: A systematic review of the literature was performed using the National Library of Medicine/PubMed database and Embase for studies relevant to preoperative diagnostic studies that predict increased risk of osteoporosis-related postoperative adverse events and if the preoperative treatment of low bone mineral density (BMD) in patients with osteoporosis improves outcome.

Results: Seventeen of 281 studies met the inclusion criteria and were included for systematic review. The task force affirmed a Grade B recommendation that preoperative osteoporosis testing with a dual-energy X-ray absorptiometry (DEXA) scan (T score <-2.5), a computed tomography (CT) scan (Hounsfield units [HU] <97.9), and serum vitamin D3 level (<20 ng/mL) predict an increased risk of osteoporosis-related adverse events after spine surgery. The task force determined a Grade B recommendation that preoperative osteoporosis treatment with teriparatide increases BMD, induces earlier and more robust fusion, and may improve select patient outcomes. There is insufficient evidence regarding preoperative treatment with bisphosphonates alone and postoperative outcome.

Conclusion: This evidence-based clinical guideline provides a recommendation that patients with suspected osteoporosis undergo preoperative assessment and be appropriately counseled about the risk of postoperative adverse events if osteoporosis is confirmed. In addition, preoperative optimization of BMD with select treatments improves certain patient outcomes.

RECOMMENDATIONS

Question:

1. What preoperative diagnostic studies predict the risk of osteoporosis-related adverse events after spine surgery?

Recommendations:

Preoperative testing with a DEXA scan T score <−2.5, a CT scan (Hounsfield Units <97.9), or serum vitamin D3 level <20 ng/mL is associated with poor bone mineral density and predicts an increased risk of a postoperative adverse event in individuals undergoing spinal instrumentation. Preoperative assessment with one of these tests (DEXA scan, CT, or serum vitamin D3 level) should be performed in patients with suspected osteoporosis. Patients with confirmed osteoporosis should be counseled regarding the potential increased risk of postoperative adverse events.
Strength of Recommendation: Grade B

Question:
2. Does preoperative treatment of low bone mineral density decrease risk of postoperative adverse event after spine surgery?
Recommendations:
Clinicians should consider preoperative teriparatide in patients with osteoporosis undergoing spinal instrumentation to decrease risk of postoperative adverse events, including screw loosening and a delayed or lower rate of fusion.
Strength of Recommendation: Grade B

There is insufficient evidence to support the use of bisphosphonates alone in patients with osteoporosis undergoing spinal instrumentation to decrease postoperative adverse events after spinal instrumentation.
Strength of Recommendation: Grade Insufficient

INTRODUCTION
Goals and Rationale
This clinical guideline has been created to improve patient care by outlining the appropriate information gathering and decision-making processes involved in the treatment of patients with preoperative osteoporosis; specifically, if preoperative identification and treatment of this metabolic bone disorder decreases risk of postoperative adverse events after spine surgery. Spinal surgical care is provided in many different settings by many different providers. This guideline has been created as an educational tool to guide qualified physicians through a series of diagnostic and treatment decisions in an effort to improve the quality and efficiency of care.

This guideline should not be construed as including all proper methods of care or excluding methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific procedure or treatment must be made in light of all circumstances presented by the patient and the needs and resources particular to the locality or institution.

Osteoporotic fragility fractures have become a major health care epidemic with the aging population, occurring in 2.1 million patients yearly.[1] The spine is affected in 245,000 patients annually, and mortality after a vertebral fracture is 22.4%, 32.7%, and 49.4% at 1, 2, and 4 years, respectively.[2] Suboptimal diagnosis and management of bone health before spine surgery can contribute to increased osteoporosis-related postoperative adverse events and unsatisfactory surgical outcomes in the elderly. These include pseudarthrosis, instrumentation complications (particularly loss of fixation at the screw–bone interface), and proximal junctional failure (PJF), with potentially catastrophic spinal fracture with or without neurologic injury.[3] The cause of

these postoperative complications may be multifactorial; however, poor bone density is often a major contributor that is potentially modifiable with appropriate preoperative diagnosis and management.

Osteoporosis can result from aging, genetic and environmental factors, certain comorbidities, and abnormal homeostasis of calcium and vitamin D metabolism. Despite the relative prevalence of osteoporosis and vitamin D3 deficiency[4,5] and various available diagnostic[6] and treatment modalities, there is a lack of consensus regarding the management of osteoporosis before spine surgery.[7] This deficiency may be related to poor understanding by many spine surgeons of bone physiology, limited cost-effective interventions, and the reluctance of spine surgeons to be the primary provider of treatment or to consult an endocrinologist. The objective of this evidence-based review is to develop guidelines for the preoperative assessment and treatment of osteoporosis in patients who are undergoing spine surgery.

METHODS

The guidelines task force initiated a systematic review of the literature and evidence-based guideline relevant to the preoperative treatment of patients with spinal disorders with osteoporosis. Through objective evaluation of the evidence and transparency in the process of making recommendations, this evidence-based clinical practice guideline was developed for the diagnosis and treatment of adult patients with various spinal conditions. These guidelines are developed for educational purposes to assist practitioners in their clinical decision-making processes. Additional information about the methods used in this systematic review is provided below.

Literature Search

The task force members identified search terms/parameters and a medical librarian implemented the literature search, consistent with the literature search protocol (see Supplemental Digital Content 1), using the National Library of Medicine/PubMed database and Embase for the period from 1946 to September 20, 2019, using the search strategies provided in Supplemental Digital Content 1.

Inclusion/Exclusion Criteria

Articles were retrieved and included only if they met specific inclusion/exclusion criteria (Supplemental Digital Content 2). These criteria were also applied to articles provided by guideline task force members who supplemented the electronic database searches with articles from their own files. To reduce bias, these criteria were specified before conducting the literature searches.

Rating Quality of Diagnostic Evidence

The guideline task force used a modified version of the North American Spine Society's (NASS) evidence-based guideline development methodology. The NASS methodology uses standardized levels of evidence (Supplemental Digital Content 3) and grades of recommendation

(Supplemental Digital Content 4) to assist practitioners in easily understanding the strength of the evidence and recommendations within the guidelines. The levels of evidence range from Level I (high quality randomized controlled trial) to Level IV (case series). Grades of recommendation indicate the strength of the recommendations made in the guideline based on the quality of the literature. Levels of evidence have specific criteria and are assigned to studies before developing recommendations. Recommendations are then graded based upon the level of evidence. To better understand how levels of evidence inform the grades of recommendation and the standard nomenclature used within the recommendations, see Supplemental Digital Content 4.

Guideline recommendations were written using a standard language that indicates the strength of the recommendation. "A" recommendations indicate a test or intervention is 2 "recommended"; "B" recommendations "suggest" a test or intervention and "C" recommendations indicate a test or intervention or "is an option." "I" or "Insufficient Evidence" statements clearly indicate that "there is insufficient evidence to make a recommendation for or against" a test or intervention. Task force consensus statements clearly state that "in the absence of reliable evidence, it is the task force's opinion that" a test or intervention may be appropriate.

In evaluating studies as to levels of evidence for this guideline, the study design was interpreted as establishing only a potential level of evidence. As an example, a therapeutic study designed as a randomized controlled trial would be considered a potential Level I study. The study would then be further analyzed as to how well the study design was implemented and significant shortcomings in the execution of the study would be used to downgrade the levels of evidence for the study's conclusions (see Supplemental Digital Content 4 for additional information and criteria).

Revision Plans

In accordance with the Institute of Medicine's standards for developing clinical practice guidelines, the task force will monitor related publications after the release of this document and will revise the entire document and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations."[8] In addition, the task force will confirm within 5 years from the date of publication that the content reflects current clinical practice and the available technologies for the evaluation and treatment for patients with perioperative spinal disease.

RESULTS

The initial literature search encompassed terms relevant to all chapters in this guideline series and yielded 6812 abstracts (5689 after duplicates were deleted). After a double-blind review, the literature review search yielded 281 abstracts for this question. Task force members reviewed all abstracts distilled from the literature search and identified the relevant literature for full text review and extraction in accordance with the Literature Search Protocol that addressed the two clinical PICO (patient/population, intervention, comparison, and outcomes) questions (Supplemental Digital Content 5). Two members of the task force initially screened all the

abstracts culled from the literature followed by all members of the entire task force who graded the best research articles that answered the two research questions. The task force graded the articles from Level I through Level IV. The Task force reviewed 281 articles, collected data on 78, and finally selected 17 articles for use in developing the chapter guidelines (Supplemental Digital Content 6).

DISCUSSION

Question

1. What preoperative diagnostic studies predict risk of osteoporosis-related adverse events after spine surgery?

Recommendations

Preoperative testing with a DEXA scan T score <−2.5, a CT scan (Hounsfield Units <97.9), or serum vitamin D3 level <20 ng/mL is associated with poor bone mineral density and predicts an increased risk of a postoperative adverse event in individuals undergoing spinal instrumentation. Preoperative assessment with one of these tests (DEXA scan, CT, or serum vitamin D3 level) should be performed in patients with suspected osteoporosis. Patients with confirmed osteoporosis should be counseled regarding the potential increased risk of postoperative adverse events.
Strength of Recommendation: Grade B

There were 11 articles that specifically addressed this question and met the inclusion and exclusion criteria. These studies primarily evaluated the predictive effect of preoperative serum vitamin D3 levels (1 study) on time to fusion and nonunion and CT and DEXA scan (10 studies) on cage subsidence, pedicle screw loosening, proximal junctional kyphosis (PJK), and outcome measures. There were no level I studies. There were 4 level II studies and 7 level III studies. There were no level IV studies included in the recommendation.

Level II Evidence

There is significant Level II evidence the relationship of osteoporosis to adverse events after spinal fusion surgery. Cho et al[9] retrospectively reviewed a 2-year series of 268 patients who underwent posterolateral fusion (PLF=182 patients) or one level posterior interbody fusion (PLIF=86 patients) to evaluate the effect of osteoporosis on patient related outcomes, fusion success, instrumentation failure, and cage subsidence. Two groups were evaluated based on their T scores: group A (non-osteoporotic: T score > -1.0 consisting of 55 patients and group B (osteoporotic: T-score < -2.5 consisting of 31 patients). The authors found that low BMI was associated with both cage subsidence (65.4% vs. 17.6%, P < 0.001) and screw loosening rates (32.3% vs.12.7%, P < 0.029). Other than osteoporosis, the groups had similar demographics except that group A had a higher average BMI, and group B had an expected higher rate of osteoporosis treatment of 48% vs. 4% (p<0.001). Although patient-related clinical outcomes did not differ between the osteoporotic patients (group B) who had cage subsidence or screw loosening and the normal BMD patients (group A), the fusion rate was lower in those that had screw loosening compared with those that did not (71.4% vs 93.9%, *P* = .038). The authors suggest that surgeons should continue to monitor screw loosening to detect a potential nonunion.

Sakai et al[10] retrospectively evaluated the mean value of the HUs inside a rectangle within the pedicle, which was defined as the HU of screw trajectory. The authors used a CT scanning model

superimposing preoperative images on the postoperative CT using 3-dimensional image analysis software. They found that the mean HU values of the screw trajectory were significantly less in the osteoporotic patient group compared with the nonosteoporotic group (147 ± 94 vs 208 ± 91, $P < .001$). The osteoporotic group was associated with increased screw loosening and was particularly a risk factor in women. The authors recommended additional augmentation with cement, hooks, or lamina taping in females with low bone density to prevent pedicle screw loosening.[10] Yagi et al[11] performed a retrospective propensity-matched study with 2 years postoperative follow-up of patients with preoperative DEXA scans. Two cohorts were compared: a moderate osteoporosis group (M group; T >−1.5) versus a severe osteoporosis group (S group: T <–1.5). They observed that BMD was a risk factor for PJF, and the incidence of PJF was significantly higher in the severe group (33% vs 8%, odds ratio [OR] 6.4 [95% confidence interval {CI} 1.2-32.3], $P < .01$). They concluded that surgeons should consider prophylactic measures against PJF when correcting adult spinal deformity in patients with low BMD.

One study included for review was not supportive of the effect of osteoporosis on spine surgery's adverse events. Yagi et al[12] in an earlier article reviewing patients with adult spinal deformity found no correlation between DEXA scan T scores of the hip and spine, and curve magnitude, fusion, and complication rates.

Level III Evidence

Ravindra et al[13] retrospectively reviewed a series of prospectively enrolled patients to evaluate the relationship between vitamin D3 deficiency (<20 ng/mL) and fusion rate. They found that nonunion at 12 months was associated with vitamin D deficiency (20% of patients with adequate serum vitamin D3 level vs 38% of vitamin D3–deficient patients, $P = .063$). In addition, multivariate analysis showed that vitamin D3 deficiency was an independent predictor of nonunion (OR 3.449, $P = .045$) when adjusted for age, sex, obesity, fusion length, location, graft type, smoking, and bone morphogenetic protein use. Finally, when the authors analyzed the vitamin D3–deficient group (<20 ng/mL) versus the insufficient group (20-30 ng/mL) versus the nondeficient group (>20 ng/mL), there was a significantly longer estimated median time to fusion in the vitamin D3–deficient group (12 vs 8.6 vs 6 months, $P = .001$). They concluded that serum vitamin D3 levels may affect nonunion rate and time to fusion.[13]

Schreiber et al[14] retrospectively reviewed postoperative CT scans at a minimum of 12 months measuring the HUs and found that the successful fusion levels had higher CT HUs than nonunion levels. The authors reported that successful lumbar fusion was associated with higher bone density both globally and within the fusion construct levels compared with patients with CT evidence of nonunion.[14] Kim et al[15] showed in a retrospectively reviewed consecutive series that patients with osteoporosis trended toward increased posterior spinous process fractures after an interspinous process device placement. There was a trend toward lower BMD in the fractures group as measured by DEXA and CT HU scans, but the association was weak.[15] Oh et al[16] performed a retrospective review of PLIF and found that BMD had a significant but weak correlation with cage subsidence ($r = 0.285$, $P < .001$). Severe osteoporotic segments (T score <−3.0) had greater risk of severe subsidence (>3 mm), but that subsidence did not cause a deterioration in clinical outcomes.[16] Kim et al[17] retrospectively reviewed a prospectively collected database of 364 patients after adult deformity surgery with 2 years' postoperative follow-up. All patients underwent preoperative DEXA scans and osteoporosis was defined as a T

score <−2.5. Osteoporosis was present in 20.4% of patients who ultimately developed PJK versus only 9.8% of patients who did not develop PJK ($P = .016$). This observation suggests that a T score <−2.5 is associated with higher likelihood of PJK in patients undergoing adult deformity surgery.[17] Puvansearajah et al[18] performed a multivariate analysis of patients with 5 years of postoperative follow-up and found that osteoporosis increases the risk of revision surgery (OR 1.98 [95% CI 1.60-2.46], $P < .0001$). More than one third (44.9%) of patients undergoing revision surgery had osteoporosis. Finally, Salzmann et al[19] retrospectively evaluated 21 patients who had long segment spinal fusion surgery (mean 5.6 levels) that included the sacrum and found a weak association between BMD as measured by a standard qualitative CT scan of the L1/L2 vertebral body. They unexpectedly found no association between sacral fractures and BMD. The study did find, however, that obese patients had a 52.4% (11/21) incidence of sacral fractures ($P = .002$)(Univariant Analysis Showed the OR 5.99, $P = .030$).[19]

Question

2. Does preoperative treatment of low bone mineral density decrease risk of postoperative adverse event after spine surgery?

Recommendations

Clinicians should consider preoperative teriparatide in patients with osteoporosis who are undergoing spinal instrumentation to decrease the risk of postoperative adverse events, including screw loosening and delayed or lower rate of fusion.

Strength of Recommendation: Grade B

There is insufficient evidence to support the use of bisphosphonates alone in patients with osteoporosis undergoing spinal instrumentation to decrease postoperative adverse events after spinal instrumentation.

Strength of Recommendation: Grade Insufficient

There were 6 articles that specifically addressed this question and met inclusion and exclusion criteria. The task force identified 3 Level II studies, 2 Level III studies, and 1 Level IV study.

Level II Evidence

Ohtori et al[20] performed a prospective, nonrandomized sequential study of osteoporotic postmenopausal females with equal BMD undergoing instrumented decompression and fusion (local autograft) for symptomatic degenerative spondylolisthesis. There were 57 females divided into 2 groups: the first 28 patients received a weekly dose of a bisphosphonate (risedronate). The next 29 patients received daily teriparatide injections. All patients were followed for 1 year and evaluated with CT scanning preoperatively and at 3, 6, and 12 months postoperatively for fusion. The rate of bone fusion in the teriparatide group was significantly higher (82% fusion rate at 8 months) than that in the risedronate group (68% fusion rate at 10 months; $P < .05$). The teriparatide group also demonstrated earlier fusion. Although teriparatide was superior to bisphosphonate regarding fusion rate and time to fusion, both groups had similar clinical outcomes.[20] Ohtori et al[21] evaluated 62 patients divided into 3 groups: 22 patients received no osteoporotic treatment (control), 20 received a bisphosphonate (risedronate), and 20 received teriparatide. They demonstrated that the incidence of pedicle screw loosening was significantly lower in the teriparatide group (7%) compared with the bisphosphonate (risedronate) group

(13%), which was similar to the control group (15%; $P < .05$) Teriparatide was also associated with increased bone mass compared with bisphosphonate.[21]

Cho et al[22] evaluated a prospective cohort of 47 patients undergoing PLIF with pedicle screws that were divided into 2 groups: the first group (23 patients) received daily teriparatide injections for 3 months which was alternated with a bisphosphonate for 3 months; the second group (24 patients) received oral bisphosphonate. Both groups underwent their respective osteoporosis treatment protocol for 1 year postoperatively. In addition to clinical outcome, postoperative T scores (DEXA scan), fusion rate, and duration to fusion (CT) were assessed. The cyclical teriparatide plus bisphosphonate group showed a significantly higher fusion rate at 6 months after surgery versus the bisphosphonate alone group (77.8% vs 53.6 %), while fusion rates were equal at 2 years postoperatively (92.6% vs 96.4%). CT follow-up at 12 months postoperatively demonstrated bridging bone in 88.9% of the bisphosphonate group and 87.5% of the teriparatide group. Screw loosening was 10.7% in the bisphosphonate group and 11.1% in the teriparatide group. Cage subsidence was 14.3% in the bisphosphonate group and 14.8% in the teriparatide group. None of these CT outcomes were significantly different between the 2 groups ($P = .374$, $P = .648$, and $P = .626$, respectively). There was no significant difference in T score between the 2 groups at 12 and 24 months postoperatively, although the teriparatide group trended toward a higher BMD (DEXA T score −3.0 vs −3.4) and earlier improvement in T scores (0.7 ± 1.4 vs 0.1 ± 0.5, $P = .013$). There was no significant difference between cohorts with respect to clinical outcomes. There authors concluded that there was no significant benefit in fusion rate and clinical outcome when adding teriparatide with bisphosphonate compared with bisphosphonate alone, but the addition of a teriparatide resulted in faster bony union and a higher BMD recovery rate.[22]

Level III

Wang et al[23] performed a retrospective comparative cohort study of 59 patients undergoing anterior cervical discectomy and fusion. Group A (31 patients) was treated for osteoporosis with calcium, vitamin D, and diphosphonate. Group B received no treatment. All patients underwent DEXA scan with osteoporosis defined as a T score <−2.5 with no baseline difference between groups ($P = .584$). The authors found that group A (osteoporosis treatment) exhibited significantly better bone mineral density (g/cm^2) than group B (no treatment) at 8.3 months postoperatively, as well as improved sagittal alignment ($P = .03$), interbody disc height ($P = .03$), and visual analog scale ($P = .03$) for upper limb pain.[23] Kang et al[24] retrospectively reviewed 97 postmenopausal women undergoing PLIF and compared 63 patients that were treated with bisphosphonates versus 34 that had no treatment. All subjects had osteoporosis as measured by preoperative DEXA scan (bisphosphonate group, T <−2.7 vs no treatment T <−2.3, $P < .001$). The authors found that bisphosphonates may negatively delay fusion short term for the first 6 months but not at 2 years postoperatively. Regardless, overall fusion rate in those treated with bisphosphonate was >80% and clinical outcomes were comparable to those who were not treated with bisphosphonate.[24]

Level IV

Kim et al[25] retrospectively evaluated 44 patients undergoing PLIF with osteoporosis diagnosed by CT. Patients were treated either with bisphosphonate (alendronate) versus no bisphosphonate. The fusion rate was similar for the bisphosphonate group (66.7%) versus the no bisphophonate

(73.9%; $P = 599$). Subjects that developed nonunion appeared to have more endplate degeneration compared with those who did not (91.3% vs 52.4%, $P = .004$). The authors concluded that alendronate does not negatively affect fusion rates in osteoporotic patients.[25]

Future Research

The lack of level I evidence is an area for improvement that would also benefit future guidelines. Future research should include randomized controlled studies to compare the efficacy of preoperative osteoporosis treatment protocols (single or multiagent), such as vitamin D3, teriparatide, bisphosphonates, and denosumab, in improving bone health and clinical outcome after spine surgery.

Conclusions

Undiagnosed and/or untreated osteoporosis can lead to potentially significant postoperative adverse events in patients undergoing spine surgery. A systematic review of the literature identified that preoperative assessment with DEXA scan (T score <−2.5), CT (HUs < 97.9) and serum vitamin D3 level (<20 ng/mL) predicted a risk of adverse events, including lower fusion rate, instrumentation failure (cage subsidence and screw loosening), and PJF. Preoperative treatment with teriparatide was associated with a higher fusion rate, earlier fusion, and lower screw loosening rates, whereas there was conflicting evidence regarding the potential benefit of preoperative bisphosphonates alone. Spine surgeons should consider preoperative assessment and treatment with these modalities in patients with suspected osteoporosis who are undergoing spine surgery and counsel patients regarding the potential risks when indicated.

Conflicts of Interest

All Guideline Task Force members were required to disclose all potential COIs before beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See below for a complete list of disclosures.

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Disclaimer of Liability
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Supplemental Digital Content 1. Literature searches

See Chapter 1: Congress of Neurological Surgeons Systematic Review and Evidence-Based Practice Guidelines for Perioperative Spine: Preoperative Opioid Evaluation for details on full PubMed and EMBASE search terms.

Supplemental Digital Content 2. Inclusion Criteria

Articles that did not meet the following criteria, for the purposes of this evidence-based clinical practice guideline, were excluded. To be included as evidence in the guideline, an article had to be a report of a study that:

- Investigated patients with cervical spine surgery, thoracic spine surgery, and lumbar spine surgery;
- Excluded patients with tumor, trauma, or infections;
- Included patients ≥18 years of age;
- Were studies that enrolled ≥80% of cervical spine surgery, thoracic spine surgery, and lumbar spine surgery (we include studies with mixed patient populations if they report results separately for each group/patient population);
- Was a full article report of a clinical study;
- Was not a medical records review, meeting abstract, historical article, editorial, letter, or commentary;
- Appeared in a peer-reviewed publication or a registry report;
- Enrolled a minimum of 20 patients;
- Was of humans;
- Was published in or after 1946;
- Quantitatively presented results;
- Was not an in vitro study;
- Was not a biomechanical study;
- Was not performed on cadavers;
- Was published in English;
- Was not a systematic review, meta-analysis, or guideline developed by others.[1]

Systematic reviews or meta-analyses conducted by others, or guidelines developed by others were not included as evidence to support this review due to the differences in article inclusion/exclusion criteria specified compared with the criteria specified by the Guidelines Task Force. Although these articles were not included as evidence to support the review, these articles were recalled for full-text review for the Guidelines Task Force to conduct manual searches of the bibliographies.

[1]The guideline task force did not include systematic reviews, guidelines or meta-analyses conducted by others. These documents are developed using different inclusion criteria than those specified in this guideline; therefore, they may include studies that do not meet the inclusion criteria specific in this guideline. In cases where these types of documents' abstract suggested relevance to the guideline's recommendations, the task force searched their bibliographies for additional studies.

Supplemental Digital Content 3.
Criteria grading the evidence

The task force used the criteria provided below to identify the strengths and weaknesses of the studies included in this guideline. Studies containing deficiencies were downgraded 1 level (no further downgrading allowed, unless so severe that study had to be excluded). Studies with no deficiencies based on study design and contained clinical information that dramatically altered current medical perceptions of topic were upgraded.

1. Baseline study design (i.e., therapeutic, diagnostic, prognostic) determined to assign initial level of evidence.

2. Therapeutic studies reviewed for following deficiencies:
    - Failure to provide a power calculation for a randomized controlled trial (RCT);
    - High degree of variance or heterogeneity in patient populations with respect to presenting diagnosis/demographics or treatments applied;
    - Less than 80% of patient follow-up;
    - Failure to utilize validated outcomes instrument;
    - No statistical analysis of results;
    - Crossover rate between treatment groups of greater than 20%;
    - Inadequate reporting of baseline demographic data;
    - Small patient cohorts (relative to observed effects);
    - Failure to describe method of randomization;
    - Failure to provide flowchart following patients through course of study (RCT);
    - Failure to account for patients lost to follow-up;
    - Lack of independent post-treatment assessment (e.g., clinical, fusion status, etc.);
    - Utilization of inferior control group:
        - Historical controls
        - Simultaneous application of intervention and control within same patient
    - Failure to standardize surgical/intervention technique;
    - Inadequate radiographic technique to determine fusion status (e.g., static radiographs for instrumented fusion).

3. Methodology of diagnostic studies reviewed for following deficiencies:
    - Failure to determine specificity and sensitivity;
    - Failure to determine inter- and intraobserver reliability;
    - Failure to provide correlation coefficient in the form of kappa values.

4. Methodology of prognostic studies reviewed for following deficiencies:
    - High degree of variance or heterogeneity in patient populations with respect to presenting diagnosis/demographics or treatments applied;
    - Failure to appropriately define and assess independent and dependent variables (e.g., failure to use validated outcome measures when available).

Rating evidence quality. Levels of evidence for primary research question[a]

Types of Studies				
	Therapeutic studies: Investigating the results of treatment	Prognostic studies: Investigating the effect of a patient characteristic on the outcome of disease	Diagnostic studies: Investigating a diagnostic test	Economic and decision analyses: Developing an economic or decision model
Level I	High-quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals Systematic review[b] of Level I RCTs (and study results were homogeneous[c])	High-quality prospective study[d] (all patients were enrolled at the same point in their disease with ≥80% follow-up of enrolled patients) Systematic review[b] of Level I studies	Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference gold standard) Systematic review[b] of Level I studies	Sensible costs and alternatives; values obtained from many studies with multiway sensitivity analyses Systematic review[b] of Level I studies
Level II	Lesser quality RCT (e.g., <80% follow-up, no blinding, or improper randomization) Prospective[d] comparative study[e] Systematic review[b] of Level II studies or Level I studies with inconsistent results	Retrospective[f] study Untreated control subjects from an RCT Lesser quality prospective study (e.g., patients enrolled at different points in their disease or <80% follow-up) Systematic review[b] of Level II studies	Development of diagnostic criteria on consecutive patients (with universally applied reference criterion standard) Systematic review[b] of Level II studies	Sensible costs and alternatives; values obtained from limited studies with multiway sensitivity analyses Systematic review[b] of Level II studies

Level III	Case control study[g] Retrospective[f] comparative study[e] Systematic review[b] of Level III studies	Case control study[g]	Study of nonconsecutive patients without consistently applied reference criterion standard Systematic review[b] of Level III studies	Analyses based on limited alternatives and costs and poor estimates Systematic review[b] of Level III studies
Level IV	Case series[h]	Case series	Case-control study Poor reference standard	Analyses with no sensitivity analyses

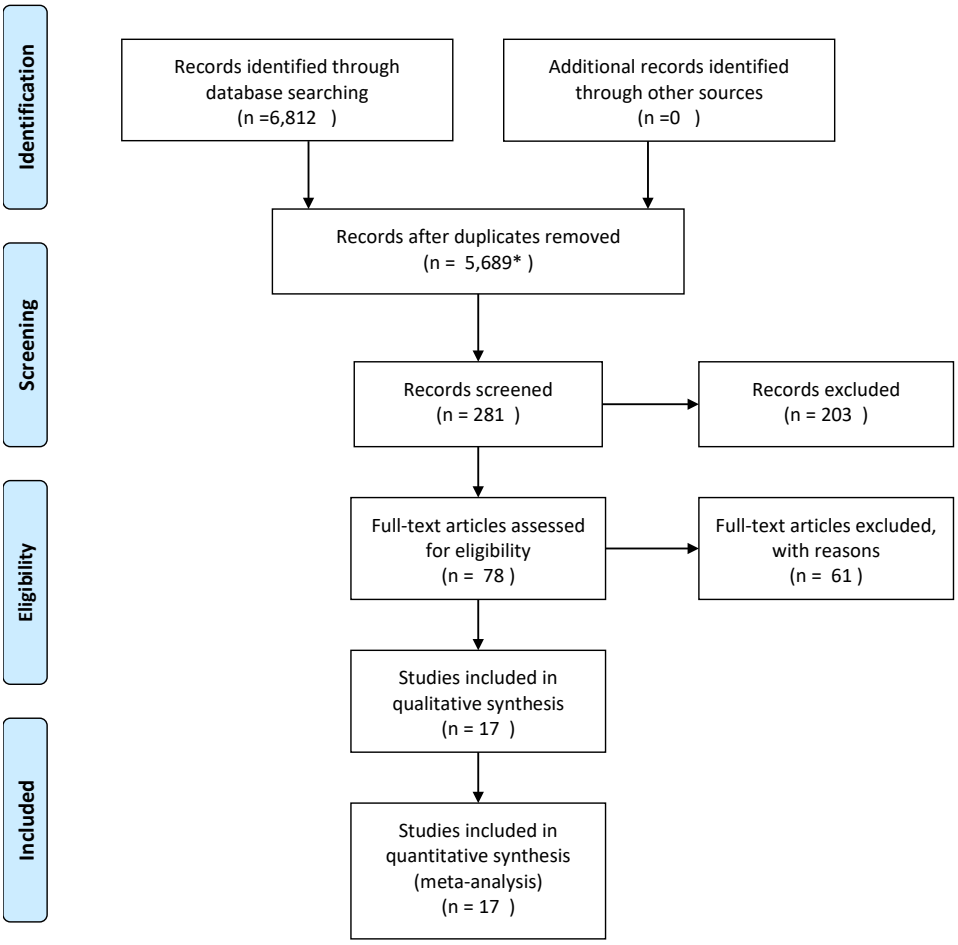
RCT, randomized controlled trial.
[a]A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
[b]A combination of results from ≥2 previous studies.
[c]Studies provided consistent results.
[d]Study was started before the first patient enrolled.
[e]Patients treated one way (e.g., instrumented arthrodesis) compared with a group of patients treated in another way (e.g., uninstrumented arthrodesis) at the same institution.
[f]Study was started after the first patient enrolled.
[g]Patients identified for the study based on their outcome, called "cases" (e.g., pseudoarthrosis) are compared with those who did not have outcome, called "controls" (e.g., successful fusion).
[h]Patients treated one way with no comparison group of patients treated in another way.

Supplemental Digital Content 4. Linking levels of evidence to grades of recommendation

Grade of Recommendation	Standard Language	Levels of Evidence	
A	Recommended	≥2 consistent Level I studies	
B	Suggested	One Level I study with additional supporting Level II or III studies	≥2 consistent Level II or III studies
C	Is an option	One Level I, II, or III study with supporting Level IV studies	≥2 consistent Level IV studies
I (insufficient or conflicting evidence)	Insufficient evidence to make recommendation for or against	A single Level I, II, III, or IV study without other supporting evidence	≥1 study with inconsistent findings*

*Note that in the presence of multiple consistent studies, and a single outlying, inconsistent study, the grade of recommendation will be based on the level of the consistent studies.

Supplemental Digital Content 5. PRISMA Flowchart



*In addition to duplicate removal, the librarian also removed strictly animal or children/adolescent studies not identified by search strategy and case reports dealing with 1 to 2 persons as encountered.

Supplemental Digital Content 6. Evidence table

PICO Question	Author, Year	Type of Evidence	Study Type	Level of Evidence	Reviewer's Conclusions
1	Cho et al., 2018[9]	Therapeutic	Retrospective comparative	II	This study affirms radiographic but negates clinical. Although higher cage subsidence and screw loosening, no difference in clinical outcomes
1	Kim et al., 2012[15]	Therapeutic	Prospective case control	III	This is a prognostic study that was downgraded because of insufficient N for power. In the setting of SP fracture after ISP device placement, there was a trend of lower BMD in fracture vs no fracture patients
1	Kim et al., 2013[17]	Therapeutic	Retrospective case series	III	This study affirms osteoporosis related to PJK and is a retrospective review with no adjusted analysis
1	Oh et al., 2017[16]	Therapeutic	Retrospective comparative case series	III	This study affirms the radiographic portion but negates the clinical. Also, indicates radiographic adverse outcomes—cage subsidence but not clinical outcome was impacted by osteoporosis
1	Puvanesarajah et al., 2016[18]	Therapeutic	Retrospective case series	III	Study affirm that osteoporosis is predictive of revision surgery in ASD
1	Ravindra et al., 2015[5]	Diagnostic	Retrospective comparative	III	Study affirms low vitamin D is associated with

					nonunion. Downgraded because of vitamin D levels assessed within 72 hours of surgery
1	Sakai et al., 2018[10]	Diagnostic	Retrospective comparative	II	Study finds that BMD and HU of screw trajectory were both associated with screw loosening
1	Salzmann et al., 2019[19]	Therapeutic	Retrospective comparative	III	Negative study finds that BMI and gender are more important risk factors than BMD for fracture after fusion
1	Schreiber et al., 2014[14]	Diagnostic	Retrospective comparative case control	III	Study affirms that successful lumbar fusion was associated with higher bone density both globally and within the fusion construct levels compared to patients with CT evidence of nonunion
1	Yagi et al., 2011[12]	Therapeutic	Retrospective comparative	II	Negative study finds no significant correlation between BMD and fusion or complication
1	Yagi et al., 2018[11]	Therapeutic	Retrospective comparative	II	Study finds low BMD is a risk factor for PJK
2	Cho et al., 2017[22]	Therapeutic	Prospective comparative	II	The study negates the use of teripratide over bisphosphonate. Although no difference in overall fusion rate or clinical outcome, the TP group had faster rate to fusion and more improved BMD scores. Negates = teripratide over

					bisphosphonate--although no difference in overall fusion rate or clinical outcome, the TP group had faster rate to fusion and more improved BMD scores
2	Kang et al., 2019[24]	Therapeutic	Prospective comparative	III	Long-term BP users have longer time to fusion but no difference in overall fusion rates at 2 years compared with nonusers
2	Kim et al., 2014[25]	Therapeutic	Restrospective comparative	IV	Study concludes alendronate does not impact fusion rates. Downgraded because of unknown patients in each group
2	Ohtori et al., 2012[20]	Therapeutic	Prospective	II	Study concludes that teriparatide had faster healing/bony union rates compared with BP
2	Ohtori et al., 2013[21]	Therapeutic	Prospective comparative RCT	II	Study affirms therapeutic teriparatide, finding administration of TP, but not BP, decreased screw loosening in patients with osteoporosis
2	Wang et al., 2016[23]	Therapeutic	Restrospective comparative	III	Study negates for ACDF. Patients with antiosteoporosis treatment had better radiographic parameters at final follow-up as well as for VAS in upper limb

ACDF, anterior cervical discectomy and fusion; ASD, adult spinal deformity; BMD, bone mineral density; CT, computed tomography; HU, Hounsfield unit; ISP, interspinous process; PICO, patient/population, intervention, comparison, and outcomes; PJK, proximal junctional kyphosis; RCT, randomized controlled trial; SP, spinous process; TP, teripratide; VAS, visual analog scale