Treatment of Spine Disease in the Elderly

Cutting Edge Techniques and Technologies

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Foreword

Advances in spine care in both technology and technique have created significant improvements in the lives of many. As the population throughout the world ages, spinal pathology affecting the elderly will become an increasingly important public health concern. Previous literature has focused on different populations, such as spinal trauma in young patients and degenerative disease in the middle aged. Older patients suffer from high rates of spinal trauma, spinal deformity, oncology, and of course progressive degenerative disease. These patients often present differently than those in younger groups. Different fracture patterns, oncological etiologies, and deformity issues are some common examples. Comorbidities increase in number and severity with age, with elderly patients requiring treatment that considers frailty and osteoporosis among other severe pathology. Elderly patients require a tailored approach to their spine care. Previous textbooks have presented the advances and current concepts of modern surgical spinal care. However, this textbook is unique in its sole focus on advances in spinal care for the elderly. The editors sought to present a comprehensive text on all aspects of spinal care in the elderly. From evaluation of the medical comorbidities and bone health to advanced techniques in pain management, physiatry, and less invasive surgical means, this text provides a reference for all of those that treat elderly patients.

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Elderly Specific Considerations in Spine Disease

The human spine is unique because of its upright posture and, as a result, is subject to predictable, progressive degenerative changes that may lead to a wide variety of pathological conditions with aging. Many of these changes are due to repetitive environmental trauma that accelerates the genetically programmed temporal aging processes of the intervertebral discs, ligaments, and facet joints. This frequently leads to loss of sagittal or coronal alignment and balance. As a consequence of the increasing elderly population, the medical community is experiencing a dramatic increase in patients with spinal disease in this age demographic (>65 years old). Aging pathology can be *intrinsic to the spine*, such as degenerative disc disease, spondylolisthesis, spinal stenosis, and adult spinal deformity, which individually or collectively frequently cause back pain, spinal cord compression, and nerve root compression. Additionally, the spine is subjected to *extrinsic causes of spinal disease* with aging including trauma and metabolic bone diseases such as osteoporosis, metastatic tumors, and infections. The purpose of this textbook is to familiarize spine surgeons with a wide variety of pathologic spinal conditions that *affect the elderly population*. These conditions often require a combination of operative and conservative treatment making it essential that spine surgeons understand the state-of-the-art techniques required to treat these conditions.

Trauma

As a consequence of aging of the spine there is a gradual loss of muscle strength, disc integrity with collapse and spondylosis/ankylosis, and misalignment. As a consequence of these changes there is a loss of flexibility and resilience of the cervical and thoracolumbar spine in the elderly when subjected to traumatic events. For example, with an aging cervical spine type 2 odontoid fractures are common and carry a high nonunion rate with bracing and may require surgery. Minor injuries of the thoracolumbar spine such as falls result in spinal compression fractures while high energy injuries result in severe fracture/dislocations, burst injuries, Chance

injuries and in the case of elderly kyphotic ankylosed spines that suffer a hyperextension injury, a complete 3 column disruption. Perhaps the most important intrinsic clinical modifier as to the type of fracture in the elderly population is the quality of the bone while there are extrinsic factors, such as metastatic tumor that has destroyed the integrity of the vertebra resulting in a pathological fracture.

Elderly patients have a broad spectrum of preexisting comorbidities that need assessment and treatment prior to surgical treatment, if feasible, since the risk of perioperative complications is higher in this challenging population [1]. For example, the treatment of odontoid fractures is controversial with more recent studies recommending open reduction and fusion [2]. Low energy compression fractures of the thoracolumbar spine account for the most osteoporotic common fractures suffered in elderly adults costing 1 billion dollars annually to treat [3]. Most require simple brace treatment or minimally invasive vertebroplasty or kyphoplasty [4, 5]. Many low-energy burst fractures can be treated with bracing but thoracolumbar ones can be quite problematic because they tend to kyphos due to lack of anterior support requiring surgical stabilization and deformity correction and potentially with anterior column support. Most demand a metastatic and metabolic work up for osteoporosis, and heal uneventfully except for a few that either have neurologic compression or develop avascular necrosis, with both conditions requiring difficult surgical reconstructions. In the case of fracture dislocations that exhibit instability or displacement, especially with neurologic injury, expedient surgical stabilization of the traumatic deformity (anterolisthesis, lateral translation, slice injury) combined with fusion and decompression should be done immediately since studies have shown improved outcomes. Hyperextension injuries in a kyphotic ankylosed spine are notoriously problematic and underappreciated. They can be very unstable, similar to ankylosing spondylitis, requiring an MRI to appreciate the 3-column nature of the injury and most likely surgical stabilization. Elderly patients often require unique surgical correction techniques to enhance fixation and address poor bone quality including concurrent vertebroplasties, hydroxyapatite-coated pedicle screws, and construct matching with less rigid titanium rods.

Tumor

Spine tumors are more common in elderly populations and can be very challenging to treat due to the patients' comorbidities, intractable back pain, possible spinal column instability, and a progressive neurologic deficit. Primary bone tumors of the spine account for less than 10% of all bone tumors with the most common type being benign vertebral hemangiomas. Far more common are metastatic spine tumors that have been reported to spread to the spine at some point during the disease process anywhere from 30% to 70% of the time. The bony spinal column is the most common site for bone metastasis with the most common cancers being breast, lung, thyroid, kidney, prostate, melanoma, and gastrointestinal (due to the larger number of GI cancers). Once diagnosed a percutaneous open biopsy is required followed by

the optional use of one of the available scoring systems which have limited value as far as prognosis [6]. Following diagnosis, an experienced multidisciplinary team is recommended to develop a meticulous treatment plan that includes various combinations of chemotherapy, radiation therapy (conventional, focused, and proton beam), and surgery. Surgery is indicated if there is sufficient vertebral column destruction to render the spine unstable and the tumor is not sensitive to chemotherapy or radiation such as a myeloma or other hematogenous tumors [7]. Another strong indication is an epidural extension of the tumor causing progressive neurologic compromise, where a prospective study has clearly shown that patients treated with direct decompressive surgery plus postoperative radiation therapy retain the ability to walk for longer duration and regain the ability to ambulate more often (ambulatory rate surgery 84% vs. radiation 57%) [8]. Surgical decompression with stabilization when required allows most elderly patients to remain ambulatory. Still, the 2-year survival rates following spinal metastasis have been reported to be 10% to 20% following diagnosis with certain cancers such as breast and prostate having a longer survival up to a 44% survival rate [9].

Adult Deformity

Degeneration of the spine is inevitable due to gradual deterioration of the discs, ligaments, and facet joints. A recent review of a Medicare database showed the overall prevalence of diagnosed spinal degenerative disease was 27.3% and increased with age [10]. These changes are subdivided into five general categories: herniated nucleus pulposus (HNP), degenerative disc disease (DDD), spinal stenosis (SS), spondylolisthesis, and adult spinal deformity (ASD). The vast majority of patients with these conditions can be treated nonoperatively with medications, bracing, physical therapy, and pain management techniques. Conditions that cannot be treated by traditional conservative treatment modalities and require surgical intervention will be discussed in the following chapters, including disc excision or artificial disc replacement for degenerative disc disease, a decompression for bony stenosis, and spinal fusion in instances of instability or deformity, and adult deformity correction.

Adult spinal deformity (ASD) is perhaps one of the most challenging degenerative spinal diseases since it involves disruption of the sagittal and/or coronal balance with pathological changes in the normal spinopelvic parameters, specifically pelvic tilt and sacral slope leading to positive sagittal balance [11, 12]. The incidence of degenerative scoliosis in the elderly ranges from 6% to 68% and is frequently associated with spondylosis, degenerative disc disease, spondylolisthesis, and spinal stenosis [13].

Surgery for ASD consists of decompression alone, posterior fusion alone, decompression with limited fusion, fusion with deformity correction, and decompression with fusion and deformity correction [13]. Anterior surgery has had a renaissance over the past decade following decades of the prevalence of posterior

spinal osteotomies which have waned in popularity and are used primarily for rigidly fused flatback deformities. The evolution back to anterior surgery has been supported by improved fusion rates and the findings that the majority of lordosis is located at L4-S1 (average 62%) which lends itself nicely to the use of hyperlordotic cages to restore lumbar lordosis in a relatively controlled manner [14]. All of these techniques will be discussed and can be used selectively or collectively to correct adult spinal deformity in concert within suggested age-adjusted goals [15].

Osteoporosis

Osteoporosis is a skeletal disease that affects over 40 million people and is defined by poor bone quality. The condition typically will exhibit low bone mineral density and has resulted in an increasing incidence of fragility fractures prevalent in the aging population. The spine is the most common site of osteoporotic fracture and unfortunately there is only a 20% chance that further assessment of the patient's bone health will be done resulting in serious morbidity and potential mortality [16]. The combined incidence of these osteoporotic fragility fractures in all locations is estimated to be 2.3 million yearly and fractures of the spine are estimated to be 700,000 annually [17, 18]. The mortality at 2 and 3 years has been found to be 32.7% and 46.1% while 20% of patients with one fracture will experience another fracture within 1 year [16–18]. Spinal osteoporosis additionally creates significant economic and medical burdens on the health care system, being estimated to be $27,500 per hospitalization and the combined cost of treatment being estimated at 17 billion dollars yearly and climbing [16–18]. Unfortunately, the condition is often underdiagnosed in elderly patients undergoing spinal reconstruction surgery and consequently it results in increased complications, increased risk of pseudarthrosis, adjacent fractures, and worse outcomes. This steadily led to a greater appreciation of bone physiology and to the absolute need to ensure optimal bone health prior to elective spine surgery by spine surgeons over the past decade [19]. As a consequence of the severe morbidity, mortality, and the cost of not treating metabolic bone disease prior to an osteoporotic fragility fracture, there has been significant emphasis on medical treatment education and a quantum leap in basic science research directed at developing effective treatment regimens to address osteoporosis. A significant need has been identified and is being addressed for the education of both primary care providers and orthopedic surgeons in the critical importance of the treatment of osteoporosis with various treatment regimens and medications. Additionally, there has been increasing implementation of diagnostic testing to identify the disease utilizing DEXA scans and the growing use of the "Surrogate" Hounsfield Units (HU) measured on CT scanning [20].

Intensive basic science research over the past two decades has resulted in the discovery of the critical cellular pathways that are responsible for normal bone physiology by utilizing both genetic analysis of normal bone metabolism and genetic abnormalities that cause bone disease to guide the development of targeted drugs to treat osteoporosis. Finally, there have been many excellent studies that have

identified the influence of Vitamin D_3 deficiency on poor bone quality on the success of fusion, instrumentation failure, and complications in adult spine surgery [21–26]. Beyond ensuring surgical patients have adequate bone density along with adequate Vitamin D_3 and calcium intake [21, 22, 26], perhaps one of the most important offshoots of osteoporotic research has been the development of targeted drug therapy to effectively treat the disease. There are currently five major classes of osteoporotic drug therapies available. The first were three catabolic compounds that slow bone resorption including the bisphosphonates in the 1990s, followed by the Selective Estrogen Receptor Modifiers (SERMs), and then Denosumab the first biologic monoclonal antibody therapy. The next were the anabolic teriparatides which are parathyroid hormone peptides and recently a second monoclonal antibody has been approved, romosozumab. This fifth osteoporotic medication blocks sclerostin activating osteoblastic proliferation promoting bone formation, while slowing resorption and does not carry a risk of promoting cancer [27–30]. These osteoporotic medications are often used with vitamin D_3, calcium supplements, and are administered sequentially to maintain efficacy. Multiple authors have also shown that vitamin D_3 combined with certain of these medications to treat osteoporosis increases fusion rates, decreases instrumentation failure, and decreases complications demonstrating their significant clinical efficacy [21, 22, 31, 32]. Understanding bone metabolism, the diagnosis of osteoporosis, and how osteoporosis influences surgical complications and outcomes is critical to promote high-quality surgical outcomes and prevent complications. Additionally, they review the current metabolic bone disease treatments available to improve bone quality, how they are incorporated into preoperative treatment regimens to improve bone quality prior to surgical intervention [33], and current surgical techniques available to improve outcomes in elderly patients with osteoporosis. In conclusion, the following chapters review the importance of understanding the treatment of tumors, trauma, adult spinal deformity, osteoporosis, and other elderly specific considerations to ensure proper treatment.

John R. Dimar II

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Contents

Part I
Special Perioperative Considerations in the Elderly

Chapter 1
Bone Health, Advances in Assessment and Treatment

Panagiota Andreopoulou

Introduction

Invasive spinal procedures that require instrumentation are performed in more than 400,000 patients annually in the United States for degenerative disc disease, spinal stenosis, spondylolisthesis, spondylosis, spinal fractures, scoliosis, and kyphosis [1–3] Cases have been increasing among patients over age 65 with otherwise long life expectancy [3] who are seeking relief from chronic pain and neurologic symptoms.

However, complications are frequent in up to 45% of cases [4–6] and are associated with substantial morbidity and healthcare costs [7, 8]. Those include pseudoarthrosis, hardware loosening and failure, proximal junctional kyphosis (PJK), graft or interbody cage subsidence, adjacent-level disc degeneration, and vertebral compression fractures [9]. A successful approach aiming to minimize risk of complications should include preoperative identification and treatment of modifiable risk factors, especially skeletal deficits that may compromise early stability of instrumentation. The precise quantification of bone strength and the treatment of compromised bone quality have been challenging for clinicians attempting to predict and optimize surgical outcomes.

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Identification of Patients at Risk for Postoperative Complications

Assessment of factors and medical conditions that may be compromising bone health is imperative in elderly patients who are planning spine surgery especially invasive procedures such as spinal fusion and instrumentation. The aging population has higher prevalence of osteoporosis due to increased bone resorption and decreased bone formation leading to decreased bone strength and high risk of fractures. In addition, the elderly are particularly susceptible to medical issues related to aging and directly affecting bone health, such as vitamin D deficiency and osteomalacia, decreased calcium absorption and other nutrient malabsorption, diabetes mellitus, primary hyperparathyroidism, paraprotein production (monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma), malignancies treated with agents adversely affecting bone mass (e.g., aromatase inhibitors for breast cancer and androgen deprivation therapy for prostate cancer), rheumatologic disorders, medications including psychotropic medications, proton pump inhibitors, anticoagulants [10], and often a long history of multiple epidural steroid injections that tend to precede spinal surgery. Therefore, a meticulous history, physical examination, and pertinent laboratory and imaging testing could unveil potentially significant concurrent medical issues that are treatable and can be corrected in time for surgery.

Osteoporosis is a skeletal condition characterized by compromised bone strength usually due to a combination of low bone mineral density (BMD) and poor bone quality, predisposing to increased risk of fracture [11]. It is a highly prevalent condition especially in women. The World Health Organization (WHO) has defined osteoporosis using a BMD score derived from DXA, that is, 2.5 standard deviations below the mean for healthy young adults at the spine, femoral neck, or total hip (T-score) [12]. T-scores between −1.0 and −2.5 are consistent with low bone mass, and those above −1.0 are considered normal.

Osteoporosis is strongly associated with increasing age and negatively affects surgical outcomes, need for revision surgery, and risk of complications. In a study of 144 spine surgery candidates over the age of 50, 27% had osteoporosis, 37.5% had evidence of prior fracture (mostly radiographic vertebral fractures), and 75% had vitamin D deficiency [13]. In a larger study of 759 patients older than age 50 undergoing spinal instrumentation at a single center, 51.3% of females and 14.5% of males had osteoporosis. Another 41.4% and 46.1% had T-scores consistent with low bone mass [14].

Another important consideration is that quite commonly skeletal quality in the spine of candidates for surgery is compromised by prior multiple epidural steroid injections (ESIs) that provide relief of symptoms of spinal radiculopathy. There is some systemic glucocorticoid absorption associated with use of ESIs [15] that is enough to cause suppression of the hypothalamic-pituitary-adrenal axis [16, 17] and hyperglycemia in patients with diabetes [18]. It has been shown that volumetric

BMD by central QCT is lower in patients receiving ESIs compared to age- and sex-matched controls [19].

Currently poor bone quality is often noted intraoperatively; therefore, risk of complications may not be optimally addressed. Standard modes of fracture risk assessment may not detect osteoporosis in spine surgery candidates, and newer methodologies are being investigated.

Dual-Energy X-ray Absorptiometry (DXA)

Measurement of areal bone mineral density (aBMD) is an assessment of the mineral content in key skeletal regions by dual-energy X-ray absorptiometry (DXA) and is the standard of care for the diagnosis of osteoporosis and fracture risk assessment. DXA is widely available at low cost with immediately interpretable results and very low radiation exposure [20]. DXA-measured BMD strongly correlated with bone strength based on biomechanical studies [21] and with fracture risk based on epidemiological studies. The risk of fracture exponentially increases as BMD decreases at the spine, hip, and forearm [22, 23]. Additionally, DXA may include an assessment of lower thoracic and lumbar (T4–L4) vertebral compression deformities via a concurrent lateral view of the spine [24].

Based on several studies, low BMD is a risk factor for PJK [25–28], adjacent fractures [28, 29], screw loosening [28, 30, 31], and hardware subsidence [32]. The stability of spinal instrumentation relies on good bone quality, and the pullout strength of pedicle screws is highly correlated with spinal BMD [33].

However, patients that are candidates for spinal fusion by definition have baseline degenerative disease (significant deformity, osteosclerosis, osteophytes, scoliosis, spondylolisthesis, degenerative disc disease, vertebral fractures, prior spine surgery) that render the spine BMD values falsely elevated and unreliable due to artifact [22, 34, 35]. Areal BMD measurements are also affected by bone size and shape, soft tissue composition, and concurrent obesity and do not allow discrimination between undermineralized bone (osteomalacia) and osteoporosis.

Assessment of bone quality by DXA in patients with lumbar scoliosis is limited [36, 37]. Younger patients with scoliosis have been shown to have low BMD [38, 39]; however, in adult patients that require surgery, many spinal segments are degenerated and sclerotic resulting in falsely normal to high BMD readings on DXA [36].

Peripheral DXA measurements of the forearm, heel, or hand BMD correlate less well with central DXA measurements and are not used in clinical practice to assess bone mass [40].

Lastly, DXA does not measure volumetric bone mineral density (vBMD) or assess bone microarchitecture that are important parameters of bone strength. Therefore, assessment of trabecular structure, cortical thickness, and focal defects must be considered for a complete risk assessment.

Computed Tomography (CT)-Based Techniques

Computed tomography (CT)-based techniques, such as use of Hounsfield units (HUs) and central quantitative computed tomography (cQCT), are emerging methods alternative to DXA for assessment of bone strength. These assessments can be performed in pre-existing CT images, thus avoiding extra radiation exposure or time commitment [41].

cQCT provides a three-dimensional measurement of vBMD in trabecular or cortical bone at the spine and hip, which is less affected by sclerotic changes, vascular calcifications [42], obesity [43], and other artifacts that compromise DXA results [44, 45]. Low BMD measurements by CT are common in patients presenting for fusion [25, 26, 28, 46, 47].

In a retrospective study of patients who underwent lumbar interbody fusion, those with pseudoarthrosis tended to have lower vBMD on postoperative CT, compared to patients with successful fusion [48]. Seventy-eight percent of patients with low BMD by CT had hardware instability, adjacent fractures, and other complications [29]. Patients with low preoperative spine vBMD not only had higher rates of postoperative skeletal complications but also earlier occurrence of complications than those with higher vBMD [47].

Another method of estimating trabecular bone BMD is measurement of Hounsfield units (HUs) of lumbar spine vertebrae in an already available CT of the spine. HUs are measured based on preoperative CT (within 6 months before surgery) from L1 to L5, in a circular region within the vertebral body, excluding cortical bone, lateral walls, endplates, or osteophytes, at the midsagittal plane, midbody axial plane, axial plane just below the superior endplate, and axial plane just above the inferior endplate [49].

A correlation between HU values and presence of osteoporosis [50–53] and success of lumbar fusion has been shown [53]. An HU value of 110 has previously been reported as a cutoff for osteoporosis [54, 55]; however, there are differences in values depending on the CT model.

Trabecular Bone Score (TBS)

Trabecular bone score (TBS) is a fairly recent advance in DXA methodology that has greatly expanded its functionality. Application of this software on the DXA spine image (TBSiNsight, Medimaps Group, Switzerland) estimates trabecular bone texture, which correlates with bone microarchitecture [56]. A relationship between 3D bone characteristics, mechanical parameters, and TBS has been established [56, 57]. TBS predicts fragility fracture risk in osteoporosis independently of BMD and of clinical risk factors and has value in monitoring response to treatment [58, 59]. TBS may elucidate the etiology of increased fractures in the setting of secondary osteoporosis with abnormal trabecular microarchitecture at a higher

BMD (e.g., diabetes, rheumatoid arthritis, glucocorticoid-induced osteoporosis). Recommended TBS reference ranges for postmenopausal women are >1.35 normal microarchitecture, 1.2–1.35 partially degraded bone, and <1.2 completely degraded bone [60].

TBS may also be falsely elevated due to spine artifact although to a lesser degree than BMD by DXA [58].

High-Resolution Peripheral QCT (HR-pQCT)

High-resolution peripheral QCT (HR-pQCT) measurement [61] involves peripheral skeletal sites that are composed predominantly by cortical bone (the distal radius and distal tibia); however, abnormal cortical bone values are associated with higher risk of vertebral fractures [62, 63]. The cortical bone rim of vertebral bodies, although thin, contributes to their bone strength [64, 65]. In a recent prospective study, abnormalities of both trabecular and cortical microarchitecture as measured by HR-pQCT were associated with the development of early complications within the first 6 months following spine fusion surgery [66].

At this time HR-pQCT is not widely available for clinical use and is mainly utilized in the research setting.

Studies suggest that higher bone mass and intact microarchitecture is critical for enabling new bone formation, increasing early hardware stability, promoting successful healing, and minimizing complications. Identification of high-risk patients prior to surgery could lead to early treatment intervention and might ultimately minimize these types of complications.

Optimization of Bone Strength Perioperatively

Deficiencies in calcium and vitamin D intake can accelerate the rate of bone loss and lead to osteomalacia.

During bone remodeling, which is a constant process throughout an individual's lifetime, calcium diffuses into and out of the skeleton. As much as 10,000 mg of calcium is filtered by the kidneys daily, and more than 98% of that is reabsorbed. Inadequate calcium intake in the setting of calcium loss by the kidneys, gastrointestinal tract, and skin can eventually lead to bone demineralization. Therefore, calcium supplementation may be indicated if dietary calcium is limited. The recommended total daily calcium intake is 1200 mg for postmenopausal women and men over age 70 and 1000 mg for men over age 50 in order to replenish the daily calcium losses (National Osteoporosis Foundation).

Vitamin D levels (25OHD) positively correlate with BMD and muscle function (e.g., walking speed). Supplementation with at least 800 IU of vitamin D daily is associated with improved balance and lower extremity function and reduced falls

[67, 68]. 25OHD levels less than 30 ng/mL are associated with secondary hyperparathyroidism, and intestinal calcium transport increases at 25OHD levels greater than 32 ng/mL.

Following a fusion surgery, endochondral and intramembranous ossification forms a solid stabilizing bony bridge across decompressed segments [69–73]; however, this process may be hindered by biological and biomechanical challenges [74].

Antiresorptive and anabolic therapies that are standard treatment for osteoporosis appear effective at improving spinal surgery outcomes and reducing complications [75]. Bisphosphonates and teriparatide have been tested in patients undergoing spinal fusion for their effects on arthrodesis, vertebral bone density, adjacent vertebral fractures, instrumentation failure, fusion mass catabolism, and graft or cage subsidence [9].

Overall, prior treatment of underlying osteoporosis is associated with lower risk of osteoporosis-related complications after spinal fusion. In a large retrospective study that included 849 patients (predominantly white (86%) females (83%) age 60–79 (80%)), treated patients and not-treated patients had 1-year complication incidence of 9.1% and 15.0%, respectively. Treated patients comprised only 14.3% of the cohort of which 88% were treated with bisphosphonates and 12.4% with teriparatide. Eighteen percent of the untreated patients with complications had to undergo a revision surgery [76].

Bisphosphonates

Bisphosphonates are the most widely prescribed treatment for osteoporosis. They are antiresorptive therapies that inhibit osteoclastogenesis in the bone marrow, decrease osteoclast activity at the bone surface, and decrease the osteoclast life span by increasing apoptotic cell death [77].

In humans bisphosphonates may be beneficial in bridging bone formation and decreasing vertebral fracture risk in patients undergoing interbody lumbar fusion but without difference in clinical outcomes. In a small prospective study, 36 patients with osteopenia undergoing single-level posterior lumbar interbody fusion were randomized to either alendronate 35 mg or vitamin D for 1 year. Fusion was assessed via radiographs and CT reconstruction. Patients treated with alendronate had a significantly higher fusion rate when compared with controls (95% vs. 65%) and decreased risk of vertebral compression fracture (VCF) (0% vs. 24%) at 1 year after surgery. Despite that, the incidence of cage subsidence, defined as more than 2 mm vertical migration from baseline on CT scan, was not significantly different between the two groups, and there was no significant difference in clinical outcome [78]. However, in another study of 44 patients, there was no difference in fusion rate between alendronate and no treatment in patients with and without endplate degeneration after posterior lumbar fusion (PLF) [79].

Two small retrospective studies looked into the effects of zoledronate intravenous infusion. The first evaluated 44 patients at 6-month follow-up after one- or

two-level PLF but found no significant difference between fusion rate, volume of fusion mass, clinical outcomes, and complications rates between zoledronate and control groups [80]. The other study evaluated 64 patients at a longer follow-up of 24 months and showed higher fusion rate (75% vs. 56%), lower risk of VCF (19% vs. 51%), cage subsidence (28% vs. 54%), and pedicle screw loosening (PSL) (18% vs. 45%) as well as significant improvement in clinical outcomes [81].

In a randomized, placebo-controlled study of 79 patients treated with zoledronic acid vs. placebo, investigators noted earlier fusion (significant difference at 3, 6, and 9 months, but nonsignificant difference at 12 months), reduced risk of VCF (0% vs. 17%), and improved clinical outcomes at 9 and 12 months post-op; however, there was no difference in overall fusion rate (82% vs. 83%). Three patients (9%) in the zoledronic acid group and five patients (14%) in the placebo group had fusion failure [82]. Similar observations were made among 30 patients receiving zoledronic acid and 34 untreated patients. No significant difference was observed between overall fusion rates at 12 months (92% vs. 92.86%), and improved clinical outcomes were observed at 12 and 24 months in the zoledronic acid group on multiple score scales. Rates of VCF (0 vs. 5 cases) and PSL (0 vs. 6 cases) were reduced in the treatment group [83].

In summary, data on effect of bisphosphonates on rate of fusion and clinical outcome measures are inconsistent; however, it appears that bisphosphonates induce earlier fusion, and reduce the risk of cage subsidence, VCF, and PSL.

Anabolic Agents: Teriparatide

Teriparatide is part of the PTH (parathyroid hormone) peptide (hPTH 1–34) [84]. Intermittent administration has an anabolic effect via the activation of osteoblast cell surface receptors that further induce the production of several growth factors, including insulin-like growth factor 1 (IGF1), and lead to primarily increase of trabecular bone mass [85].

Several small and mostly retrospective studies have demonstrated a beneficial effect of teriparatide treatment on fusion outcomes [86–92].

Higher fusion rate was noted 6 months after PLF or transforaminal lumbar interbody fusion (TLIF) in 29 patients treated with teriparatide monotherapy compared to 37 untreated patients (69% vs. 35%). However, there was no significant difference in Japanese Orthopedic Association Pain Evaluation Questionnaires (JOA-BPEQ) or ODI scores between the two groups [92].

Sequential/cyclical treatment was studied in 47 patients after PLIF for spinal stenosis who were treated with 3 months of teriparatide alternating with 3 months alendronate for a total of 12 months compared to risedronate alone for at least 12 months. The first group had earlier fusion (6.0 ± 4.8 months vs. 10.4 ± 7.2 months) and improved BMD recovery range (T-score) at 24-month follow-up compared to alendronate alone (0.7 ± 1.4 vs. 0.1 ± 0.5). However, again no significant difference

in ODI, VAS, or Prolo scale scores was observed at 24 months, and no significant difference in overall fusion rate (92.6% vs. 96.4%) [93].

Anabolic therapy is likely superior to antiresorptives in the setting of spinal fusion surgery. In a study of 57 patients treated either with teriparatide starting at 2 months preoperatively and continuing for 8 months postoperatively or with risedronate, earlier fusion and higher fusion rate was noted at 12 months after one or two-level PLF (82% vs. 68%). However, there was no significant difference in low back pain or lower extremity pain [86].

Teriparatide was shown to be superior to bisphosphonate in reducing the incidence of PSL in 62 postmenopausal women treated with teriparatide for 2 months preoperatively and 10 months postoperatively after one- or two-level PLF compared to risedronate and to untreated patients, based on radiographic and CT analysis (7–13% vs. 13–26% and 15–25%). Unlike other bisphosphonates, risedronate did not significantly reduce the rate of PSL [88]. It appears however that any benefit of teriparatide in reducing PSL is significant after the first 6 months post-op as observed in 84 patients treated with teriparatide for 6 months post-op followed by risedronate compared to patients treated with risedronate monotherapy. In that group the number of loosened screws detected between 6 and 12 months was significantly different (2.3% vs. 9.2%) despite the opposite effect early on after surgery [89].

A retrospective clinical review of 159 patients from 27 different centers in Japan undergoing instrumented fusion for osteoporotic vertebral fracture showed a lower rate of mechanical complications (BP vs. TP: 73.1% vs. 58.2%) in those receiving postoperative teriparatide therapy for 2 years vs. those receiving oral bisphosphonate therapy [94]. However, a placebo-controlled trial in patients with PMO undergoing non-instrumented PLF showed no radiographic or clinical improvements with teriparatide initiated immediately postoperatively [95].

In summary teriparatide use is associated with earlier fusion, higher overall fusion rates in some but not all studies, and reduced PSL compared to bisphosphonates. Data regarding potential higher benefit with treatment starting preoperatively are lacking, and this is problematic given the frequent dilemma regarding timing of surgery and need for potential delay in order to treat underlying osteoporosis.

Anabolic Agents: Abaloparatide

Abaloparatide is a peptide analog of PTH-related protein (PTH-rP) and thus a PTH receptor agonist with stronger affinity compared to teriparatide. It increases bone formation in women with postmenopausal osteoporosis, leading to greater increases in spine BMD compared to teriparatide during the first year of therapy and an overall 86% reduction in vertebral fracture risk compared to placebo [96].

In a rat posterior lumbar fusion model, treatment with abaloparatide was associated with improved fusion mass architecture by micro-computed tomography (micro-CT), and a onefold higher fusion rate compared with vehicle, although the latter was not clinically significant [97].

A recent case report of a 66-year-old woman with cervical fusion nonunion and two failed revision surgeries showed successful fusion after 12 weeks of abaloparatide therapy, starting 2 weeks prior to corpectomy and fusion [98].

Combination Therapy

A novel approach in the treatment of osteoporosis is the combination of anabolic agent with a potent antiresorptive. The later addition of denosumab to teriparatide treatment has been shown to be highly effective in reducing risk of fractures [99]. Denosumab is a RANKL inhibitor and the most potent antiresorptive available. The same approach may be useful in the setting of spinal surgery. In a small clinical trial, 16 patients with osteoporosis and lumbar spinal stenosis were randomized to treatment with teriparatide alone (starting a month before the surgery and continued for 12 months after surgery) vs. teriparatide and denosumab (administered at 2 months and 8 months postoperatively). All patients underwent posterior lumbar interbody fusion with local bone grafts. Femoral neck BMD and bone turnover markers were measured at 3, 6.9, and 12 months following surgery and fusion rates assessed via CT at baseline, 6, and 12 months postoperatively. The combination group had a higher fusion rate at month 6 compared with patients receiving teriparatide alone [100].

Overall, there is insignificant difference in short-term clinical results despite radiographic union [101]. However, in the long term solid union is associated with better functional outcomes [28].

Conclusion

Whereas the great majority of candidates for spinal surgery have underlying poor bone quality, several advances in preoperative fragility assessment via imaging as well as treatment modalities to improve bone strength are available and allow us to optimize surgical outcomes.

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