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The aging spine: new technologies and therapeutics for the osteoporotic spine

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Abstract Osteoporosis results in low-energy fractures of the spine. The load necessary to cause a vertebral fracture is determined by the characteristics related to the vertebral body structure, mineral content, and quality of bone. Radiographic techniques centered on dual X-ray absorptiometry (DXA) permit a determination of bone mass and fracture risk. Current medical therapies principally using bisphosphonate and pulsatile PTH profoundly decrease the risk of fracture (50+%). Fall prevention strategies can further decrease the possi-

bility of fracture. A comprehensive approach to osteoporosis can favorably alter the disease.

Keywords Vertebral fracture · Osteoporosis · Bisphosphonates · PTH (1–34) · Falls

Introduction

Osteoporosis is a serious problem in the United States, affecting as many as 13–18% of women and 3–6% of men [49, 55, 64, 68, 89]. If untreated, it is estimated that more than half of all Caucasian white women will sustain an osteoporotic fracture during their lifetime [16, 89]. Approximately one-half of these fractures are related to the vertebral bodies, with two-thirds being silent and one-third symptomatic. Epidemiological studies have demonstrated that multiple vertebral fractures increase morbidity [67, 69], and the presence and increasing numbers of fractures significantly increase mortality rates [11, 23, 41, 48]. Despite the recognition that osteoporotic fractures increase the risk for additional vertebral fractures as well as hip fractures, the majority of individuals with these fractures remain undiagnosed and untreated [28, 31, 74].

Over the last ten years, great strides have been made in understanding the pathophysiology of osteoporotic vertebral fractures. Radiographic methods have been enhanced to aid in the diagnosis of osteoporosis. New therapeutics

have been developed that may decrease the fragility fracture rate by up to 50% compared with controls treated only with calcium [7, 24, 40, 70, 79]. During the same time period, two minimally invasive procedures have been developed to rapidly address painful vertebral fractures – vertebroplasty and kyphoplasty. Details regarding these procedures are the subject of separate articles within this issue.

Fracture etiology: factor of risk

Vertebral bodies sustain fractures under two different mechanical environments: repetitive loading that fatigues the cancellous bone and leads to the accumulation of microfractures, or single traumatic events may overload the vertebral body and lead to fracture [58]. To understand the etiology of vertebral fracture, information about the loads imposed onto the vertebral body and the load-bearing capacity of the vertebrae at the time of risk need to be quantified. This concept has been defined as the factor of risk, and represents the ratio of the load applied to the bone over the load necessary to cause a fracture [42]. The load

necessary to cause a vertebral fracture is determined by the characteristics related to the vertebral body structure and mineral content.

The determinants of bone failure load

The ability of the vertebral body to bear certain loads depends on both the material properties of the bone and on the geometrical distribution of the tissue components which are able to withstand load [39]. Vertebral fractures occur in cancellous bone, which has a complex microstructure. The volume of tissue contained within cancellous bone is the “bone volume fraction,” and the mass of the bone tissue within a given volume is the “apparent density.” The cancellous apparent density is directly related to the load-bearing capacity of the bone, and the ultimate stress which represents the failure load per cross-sectional area is proportional to the square of the apparent density [9]. However, two regions of apparent density can differ substantially in ultimate stress as a result of trabecular microarchitecture. The ultimate stress along the superior to inferior direction is twice that of the medial-lateral or anterior-posterior directions [30]. Presently, noninvasive methods to accurately characterize the trabecular morphology are in development.

The final contributor to bone strength is the material properties of the tissue. Local changes in collagen matrix cross-linking, such as occur in osteogenesis imperfecta, or changes in mineral content, such as occur in osteomalacia, are known to affect the material properties. While the altered bone material properties can be determined invasively through chemical analysis, they can often be implied by patient characteristics and clinical laboratory tests. Overall, the strength of the vertebral body is related to the bone mass, the macroscopic and microscopic distribution of the bone mass and the material properties of the composite bone.

Diagnosis of osteoporosis

Radiographic methods

Commonly used in vivo imaging techniques do not capture cancellous bone volume fraction and architecture. Therefore, assessment of bone density occurs at the whole bone level. Areal bone mineral density (g/cm^2), measured by dual x-ray absorptiometry (DXA), is a single measure that captures both mineral content and bone size [10]. Studies have reported good correlation between bone mineral density, as measured by DXA, and vertebral body failure load [71]. There is a higher risk factor of fracture for a similar load as the bone density decreases. Numerous clinical studies have demonstrated that low bone mineral density is associated with increased fracture rates for the spine [66].

The DXA scan can be performed in a lateral or anteroposterior (AP) mode. The sagittal view is highly accurate and correlates well with fracture risk [13, 93]. However, with the presence of osteophytes and scoliosis, the precision decreases and may be artificially elevated, particularly with osteosclerotic facet joints [62]. Above the age of 60, lateral DXA avoids the posterior elements of the spine, and may address this problem in patients typically with evidence of osteoarthritis of the spine. However, the overhanging ribs and the superior projection of the iliac wing often obscure the L1 and L2, and L4 and L5 vertebral bodies, respectively, leaving one or two vertebral bodies available for analysis. This may significantly decrease the precision of the methodology. As a consequence, in patients over 60, attention is often directed to the hip, where both the femoral neck and the total femur have excellent correlation with vertebral fracture risk [51]. Since the hip has a greater content of cortical bone, there may be a lag time between bone mineral density and recent bone loss [63, 76]. Similarly, a comparable lag time may occur in demonstrating improved bone stock as a consequence of medical interventions.

Vertebral morphometry, which involves quantification of the vertebral height and shape, has been used to evaluate early vertebral deformities. These measurements have traditionally been accomplished using lateral radiographs of the spine [36]. An important advance in DXA imaging includes the “instant vertebral assessment” (IVA) technique, also termed “morphometric X-ray absorptiometry” (MXA). This allows visualization of both the lateral and AP views of the spine from T4 to L4 [37, 26], and is a new method for quantifying vertebral deformities. There is a close correlation with radiographic evaluation of the spine, and this supplement may detect early fractures. Comparison with standard X-ray has shown a precision error of approximately 2–3% [3, 27, 86]. Vertebral height measurement is also significantly associated with bone mineral density [5]. The scoliosis and kyphosis angles can be measured for spinal segments, but placing the patient in the prone position can often lead to an underestimation of the true kyphosis. Scoliosis is affected to a lesser degree, particularly in the elderly. MXA is a relatively fast, low-radiation technique to identify prevalent vertebral deformities, particularly moderate to severe deformities of the middle thoracic to lumbar spine. It has a high correlation to the gold standard lateral X-ray, and can be obtained using a DXA machine with a single image [25, 26, 85].

Quantitative computed tomography (QCT) measures volumetric bone mineral density of trabecular bone [32, 46], but has poor precision due to increasing fat content in the marrow of older patients. This technique is also technologist-dependent, with high variability depending on the site chosen for analysis. It has twenty times the radiation of a DXA scan, and its current use is mainly in the research setting.

Laboratory measurements

Laboratory studies used to assess quality and quantity of bone tissue in the spine are centered on bone marrow abnormalities (complete blood count, sedimentation rate, serum and urine immunoelectrophoresis); endocrinopathies (hyperthyroidism, hyperparathyroidism, type I diabetes mellitus, Cushing's disease); and osteomalacia (25-hydroxy-vitamin D, bone alkaline phosphatase, intact parathyroid hormone, serum calcium and serum phosphate) [4, 94]. This latter group represents bone collagen breakdown products and may be further evaluated using urinary N-telopeptide, pyridinoline peptide, dehydroxypyridinoline peptide, or serum c-terminal peptide. These markers identify elevated bone turnover, which directly increases fracture risk, and also screen for individuals with collagen variance, which often have very low parameters of bone turnover, such as osteogenesis imperfecta [2].

Treatment modalities

Osteoporosis has been divided into high-turnover and low-turnover osteoporosis. The most common form is high-turnover post-menopausal osteoporosis, in which osteoclast resorption is accelerated. Bone formation is compromised in low-turnover osteoporosis. Several families of agents have been suggested and developed to address the high-turnover state, including estrogen, selective estrogen receptor modulators (SERMs) such as raloxifene, calcitonin and bisphosphonates. Although calcium and vitamin D are not considered anti-resorptive agents, approximately half of patients presenting at hospitals with hip fractures show evidence of calcium deficiency and secondary hyperparathyroidism [75, 91]. Therapeutic physiologic levels of calcium and vitamin D (1500 mg of elemental calcium, 400–800 units of vitamin D) have been shown in a series of studies to significantly decrease osteoporotic fractures in the elderly population, primarily by reversing secondary hyperparathyroidism [19, 87].

Estrogen is an anti-osteoporotic agent, and has been shown to increase bone mass while effecting a decrease of vertebral fracture incidence by approximately 50% [54, 60]. Unfortunately, estrogen in combination with progesterone therapy is associated with increased cardiovascular disease, initiation of dementia and a small rise in the risk for breast cancer. As a consequence, estrogen is mainly used in the early post-menopausal period to treat post-menopausal symptomatology, and then lowered to the least effective dose to control symptomatology [54]. It is no longer recommended by the US Federal Government for the treatment of osteoporosis [96].

SERMs, particularly raloxifene, are anti-resorptive agents which have a significant anti-estrogen effect on breast tissue. However, osteoblasts are preferentially stimulated by SERMs and upregulate the rate of bone forma-

tion. Consequently, raloxifene has been shown to be an effective anti-resorptive agent in the treatment of osteoporosis [24]. Post-menopausal use decreases vertebral fractures by approximately 40% and increases spinal bone mass [92]. Unfortunately, similar protective effects have not been demonstrated in preventing hip fractures [20, 24]. Early data suggest that raloxifene decreases the risk of breast cancer by 70% [12, 21], which was an early indication for this agent. However, by stimulating estrogen receptors, raloxifene similarly increases the risk of pulmonary emboli and thrombophlebitis and may cause profound post-menopausal symptomatology. In light of the fact that it has no protection against hip fractures, raloxifene is not considered a primary treatment for osteoporosis.

Calcitonin is an intranasal agent which has shown moderate protection against spine fractures, with an incidence decrease of 33% in one series [15]. However, it has little to no effect on preventing hip fractures. There are some controversial data suggesting that calcitonin may relieve bone pain through an unknown mechanism. Its current use is in alleviating painful vertebral fractures as a consequence of osteoporosis, and only as a secondary antiresorptive agent. It should be terminated as soon as pain has been controlled, as other agents are much more successful.

Bisphosphonates include alendronate and risedronate, both oral agents, and zoledronic acid and pamidronate, given intravenously. These agents have been shown to be extremely efficacious in high-turnover osteoporosis [43]. Bone turnover is rapidly decreased within 6 weeks with the oral agents and within 3 days with the intravenous drugs. They increase bone mass at all measurable sites and decrease fracture incidence by 50%, including in the spine and the hip [7, 18, 57]. Bisphosphonates' mechanism of action involves interposition between osteoclasts and Howship's lacunae, thus interfering with resorption. The drug is then ingested by the osteoclast and disrupts cellular membrane synthesis pathways, leading to the osteoclasts' premature death [80]. Reported side effects of oral bisphosphonates include esophagitis and indigestion, but the once weekly regimen appears to be better tolerated and just as efficacious as daily dosing [65, 38]. Intravenous therapies, while not tested specifically for treatment in osteoporosis, appear to be efficacious, and once yearly zoledronate (Zometa) infusions appear to be just as effective as the oral dose of alendronate regarding bone mass [22]. Prospective fracture risk data are still lacking.

Bisphosphonates decrease bone turnover, and in very high dosages in canine models have been shown to cause fatigue fractures that are not actively repaired. Recent data indicate that patients on alendronate for 10 years have an 8.6% fracture rate in the first three years and 8.1% in the last five years, while the placebo group has a 19.6% fracture rate [61]. Patients stopping alendronate therapy after 5 years retain the decreased fracture risk. This suggests that bisphosphonates remain active for extended periods once the bone surface has been coated. The half-lives of

alendronate and risedronate are at least 10 years and 1.5–3 years, respectively.

Fracture healing with bisphosphonates has been studied in animal models, and although callus remodeling was somewhat delayed, the ultimate mechanical strength of the repaired bone was unchanged compared to the controls [84]. There are no published data reporting the effects of bisphosphonates on spinal fusions. Overall, bisphosphonates are extremely effective in the prevention of osteoporotic fragility fractures. In addition, bisphosphonates are just as efficacious in men as in women [1, 35, 78], and are particularly effective in preventing steroid-induced osteoporosis [14, 90].

The medications discussed to this point are aimed at inhibition of osteoclastic bone resorption, and fracture protection is afforded by the avoidance of significant bone mass loss. However, in low-turnover osteoporosis, the primary disturbance is ineffective osteoblast activity. Anabolic agents lead to bone mass accretion at a high rate. Parathyroid hormone (PTH 1–34) has been recently released for the treatment of osteoporosis. It can lead to up to a 13% increase in bone mass within a year of therapy, and appears to have protection against fractures, although possibly slightly later than the bisphosphonates [8, 17, 27, 29, 45, 73]. PTH is given by a self-administered subcutaneous dose. Appropriate serum levels of PTH stimulate osteoblasts preferentially, and do not lead to increased osteoclastic resorption.

As the cellular and genetic pathways activated by PTH are elucidated, other benefits of PTH have been proposed. Several articles report on the possible benefits of PTH on augmentation of fracture healing [44, 47, 72, 77]. Callus formation was accelerated by the early stimulation of proliferation and differentiation of osteoprogenitor cells and increases in production of bone matrix proteins [72]. There are no data at this time answering the question of whether PTH will play a role in enhancing spine fusion, though similar mechanisms may be involved. For high-turnover states, controversy exists as to the indications of PTH versus the bisphosphonates. Currently, we recommend bisphosphonates within the 1st year to impede the high osteoclast activity. Patients with low-turnover states, patients who have been on bisphosphonates and have further fragility fractures, or patients who have radiographic evidence of loss of bone mass would be candidates for PTH. Parathyroid hormone is acceptable in women of child-bearing age. Concerns of osteogenic sarcoma have been voiced regarding PTH due to PTH-like receptors on osteosarcoma cells. Therefore, PTH is not recommended for patients with higher rates of osteoblast activity, such as children, patients who have undergone radiation, or patients with Paget's disease [6, 34, 83].

Fall prevention

Patients with osteoporosis who sustain one or more falls within a year have a 25-fold higher risk of fracture [33].

Though hip fractures are typically considered the greatest cause of morbidity in osteoporotic patients following a fall, up to 15% of vertebral fractures are associated with falls and account for significant morbidity [50]. Therapeutic medications do not completely eliminate fractures, and furthermore these often take between 6 months to 1 year to become effective. Therefore, fall prevention becomes a critical factor in fracture prevention [81, 98]. Fall history can be determined through a complete patient interview, as can the inability to rise from a chair without using the hands, poor eye sight and neuromuscular impairment. Osteoporotic individuals without vertebral compression fractures have single-limb stance times ranging from 13 to 15 s [59]. Another easily administered and highly informative test is the heel-toe straight line walk. When considering the etiology for increased falls, a wide variety of factors must be considered, including neurologic, metabolic, ophthalmologic, vascular and cardiac contributors. The interplay of these factors to cause increased falling may best be evaluated in the hands of a neurologist, physiatrist, or a clinician with similar interests.

Fall prevention is achieved by balance training [98]. While therapeutic exercises for bone mass accretion focus on load bearing exercises [95], balance training utilizes a different array of activities. Enhancement of muscle coordination through water therapy and games, particularly racquet games, which require movement in different directions, have been successful. Tai Chi programs for fall prevention were first described by Wolf et al., who reported a decrease in falls by 47.5% and a similar subsequent decrease in fracture risk [100]. Its efficacy has been confirmed more recently [53, 101]. At the Hospital for Special Surgery, our Tai Chi program has been extremely well received, and 1-year follow-up has indicated that the majority of patients continue to perform Tai Chi after they graduate from the class. Regarding the fracture risk with exercise programs, as bone mass decreases, loads applied anterior to the center of gravity become more deleterious. Relatively heavy weight-lifting should be discouraged in patients with osteoporosis, and sit-ups or crunches should be avoided. Patients should rely on isometric exercises to strengthen abdominal musculature.

The characteristics of surfaces are extremely important, as many vertebral fractures occur with falls. Carpets and soft surfaces are suggested for individuals with a predisposition for falling. In addition, for nursing home patients with dementia or who are otherwise disoriented, floor surfaces adjacent to their beds must be closely scrutinized.

Future interventions

Recent investigations have suggested several local and systemic procedures that may lead to rapid restoration of vertebral body bone mass and architecture. The first group includes direct intervention in a high-risk vertebral body,

such as a vertebral body adjacent to a fusion, between two vertebral fractures, or at a site of acute kyphosis. Potential agents include the bone morphogenetic proteins (BMPs), which have been demonstrated to lead to rapid bone augmentation, specifically BMP-2 and its analog receptor agonists [82, 102]. These agents may be placed directly in trabecular bone and can rapidly lead to enhanced bone mass, possibly by up to 30% within 6 weeks. The mechanical properties of this bone, however, will be shaped by the mechanical load applied to that vertebral body in the following weeks to months. Local bone regeneration using this technique can be maintained by systemic agents, including bisphosphonates and PTH.

The second area involves the use of gene therapy. Most growth factors and medications, even with slow release, are metabolized and excreted within a relatively short period of time. Lieberman and others have demonstrated that the utilization of a BMP gene can continue the production of BMP-2 over a long period of time, controlled by the promoters within the inserted gene [56]. Whether the gene is ideally transduced through a viral vector or through ex vivo insertion into appropriate cells is uncertain, but this technique appears promising [88, 99]. It may be possible to insert cells containing gene therapeutics which will preferentially direct bone metabolism in osteoporotic vertebral sites. There is preliminary evidence in animal models that intravenous injection of specialized cells can be targeted to the site of the fracture and then allow the incorporated genes to produce their bone augmentation products.

Aside from activating biological systems to stimulate bone formation in vivo, a family of biodegradable ceramics has been established that can lead to mechanical bone augmentation. They may be injected into vertebral bodies, and because the size of their trabecular structure is similar to human bone, they are gradually resorbed and replaced by native bone over time [52, 97]. The calcium sulfate and tri-calcium phosphate classes are more resorbable than bone cements such as polymethylmethacrylate, but will still lead to mechanical protection for a period of years.

Osteoporotic vertebral fractures occur commonly and lead to long-term morbidity and mortality. Biomechanically, they result from the structure, mass and material quality of cancellous bone. There are diagnostic tools available which allow the clinician to recognize osteoporosis and to further classify the underlying etiologies. Many US Food and Drug Administration (FDA) approved agents now exist to address either the high-resorptive rate or the low-formation state successfully, and have been shown to decrease the vertebral fracture rate. Patients presenting with a fragility vertebral fracture require osteoporosis evaluation and treatment, because further fractures in both the spine and the hip will occur in the majority of individuals who remain untreated. New methodologies on the horizon include local and systemically administered substances, including cements, proteins and genes which may rapidly augment vertebral bone quality.

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