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REVIEW

The Case for Bone Health

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ABSTRACT

Fractures occur more readily in people whose bones are osteoporotic. The orthopedic surgeon may not have the time to explore the etiology of each fracture that must be repaired. To minimize the risk for fracture recurrence it is helpful to the patient to undergo an assessment of bone to determine the degree of bone loss as well as its underlying causes. Bone density assessments and fracture risk assessments using the FRAX tool are two ways to go about this in the clinic. Assessment of blood concentrations of vitamin D, parathyroid hormone, and minerals such as calcium, phosphorus, and magnesium, can help provide an underlying mechanism of bone loss and can lead to appropriate medical management.

INTRODUCTION

Orthopedic surgery is a highly demanding specialty. It requires consummate surgical skill in the learning and performance of complex operations designed to repair bones, joints, ligaments, and tendons in order to assure the patient an optimal quality of life. The number of patients seeking orthopedic help combined with the time taken to perform labor-intensive procedures assures that the orthopedic surgeon will be fully occupied in the performance of these tasks. Therefore, when patients present to the orthopedic surgery service with recurrent fracture it is quite understandable that an investigation into the cause of the fracture is not undertaken.

For this reason patients who experience recurrent, or even initial, fracture, are referred to their primary care physician upon hospital discharge and in general the concern in ambulatory visits to the orthopaedic clinic is ensuring that the patient's recovery from surgery is uneventful and consistent with state-of-the art management.

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BONE LOSS

There remains an underlying problem, however, in that fractures occur more readily in those patients who have experienced bone loss. The process occurs commonly in postmenopausal women, in the elderly

of both sexes, and in people of any age with a genetic mutation or chronic inflammatory disease, and perhaps others as yet unidentified. Bone loss can occur as a result of increased bone resorption, reduced bone formation, or the simultaneous occurrence of both.

Moreover, bone loss is clinically silent, in a manner akin to high blood pressure or glaucoma. Therefore, it must be actively searched out by screening methods because the first manifestation is likely to be a fracture. Thus, when orthopedic surgeons treat patients with fracture, especially low-trauma (fragility) fracture, they should be aware that if the cause of the fracture remains undetermined there is a significant likelihood of a second fracture.

TOOLS USED IN THE DIAGNOSIS OF BONE LOSS

The chief tool currently available to diagnose bone loss is dual-energy X-ray absorptiometry, or DEXA. This is a technique in which two X-ray beams, one of high energy and the other of low energy, are passed through a region of interest such as the hip or lumbar spine. The degree of attenuation of the X-ray beams as they pass through hard tissue is then converted to bone density and expressed as a two-dimensional projection of bone mineral density at that site. Thus, the formula for bone mineral density (BMD) is the quotient of bone mineral content (BMC) in grams divided by bone area (BA) in square centimeters. The amount of radiation from a DEXA study is about the equivalent of that from a chest X-ray. The bone densitometer contains software programs for adults and, separately, for children that calculate the number of standard deviations from peak bone mass in young adults (the T-score) and the number of standard deviations from age- and sex-matched normal values (the Z-score). Extensive studies have been performed on the value of T-scores in predicting fractures in adults and it is now established that each standard deviation below the young adult peak bone mass doubles the risk for fracture. From these data, the World Health Organization classified bone loss in adults into two categories of severity. A T-score ranging from –1 to –2.5 is classified as osteopenia, while a T-score below –2.5 defines osteoporosis.

A T-score cannot be used to define osteoporosis in children. Were the T-score employed in this fashion, every child ever born would have osteoporosis. Hence, the International Society of Clinical Densitometry in 2007 established a working definition of pediatric osteoporosis, although it is subject to revision. The definition requires both a Z-score of –2.0 and an existing fracture. Therefore, unlike the case in adults, pediatric osteoporosis cannot be diagnosed by DEXA alone.

The other useful tool in adults, once bone density is known, is FRAX. This tool was developed by the World Health Organization Collaborative Group based primarily at the University of Sheffield in the United Kingdom. The FRAX tool is an on-line questionnaire that examines risk factors for fractures, including family history of osteoporosis, smoking, alcohol consumption, use of glucocorticoid medication, diagnosis of rheumatoid arthritis, and anthropometrics along with DEXA scores to calculate the 10-year risk for a hip fracture and the risk for developing other fragility fractures. The questionnaire is country specific and can be accessed on-line by use of Google or simply going to the website: http://www.shef.ac.uk/FRAX.

In pediatrics the problem is not so straightforward inasmuch as children are continuing to grow and to be subject to both bone modeling and remodeling. Therefore, the lack of the true third dimension poses the problem of accurate assessment of bone density by DEXA. Furthermore, DEXA, by its nature, tends to over-read BMD in larger bones and under-read BMD in smaller bones. Thus, in pediatrics true volumetric bone density as determined by peripheral quantitative computed tomography (pQCT) might have an advantage. Using central CT would cause a radiation safety problem for routine use in children.

Another problem with DEXA is metal. Metal objects, such as rods, screws, and even staples, will invalidate DEXA measurements. Thus, DEXA is an imperfect diagnostic tool but is widely available and easy to use.

CAUSES OF CHRONIC BONE LOSS

There are many causes of chronic bone loss. The most widely appreciated is loss of estrogen and testosterone with aging, but also chronic inflammatory conditions, such as rheumatoid arthritis, inflammatory bowel disease, and collagen vascular disease, can result in bone loss. This is because chronic inflammatory conditions result in excessive cytokine production; especially interleukins (IL)-1β and IL-6 which stimulate the receptor activator of the nuclear factor κB (NFκB) ligand, abbreviated as RANKL, which in turn stimulates marrow stem cells to differentiate into osteoclasts. The stress response entails endogenous catecholamine and glucocorticoid production with consequent reduction in osteoblast differentiation and osteoblast and osteocyte apoptosis.

PHARMACOTHERAPY

To combat chronic bone loss, a variety of drugs are available to treat excessive bone resorption, and one drug is on the market as an effective anabolic agent with another in clinical trials. The anti-resorptives consist of N-containing bisphosphonates for oral or intravenous use and a monoclonal antibody directed against RANKL for subcutaneous use. Currently in clinical trial is a cathepsin K inhibitor, which is a monoclonal antibody against a resorptive enzyme liberated by osteoclasts.

The bisphosphonates once in the body are removed by the bone on first pass and are taken up by the bone matrix. Osteoclasts in the area will take in the bisphosphonates by endocytosis. Once inside the osteoclast the bisphosphonates inhibit the enzyme farnesyl pyrophosphate synthase. This enzyme is critical in the cholesterol biosynthetic pathway and its inhibition disrupts the cell membrane structure of the osteoclast. The result of this disruption is defective signaling pathways that originate at the cell membrane. The consequence of the disordered signaling is apoptosis of the osteoclast. A monoclonal antibody against RANKL, denosumab, will interfere with osteoclastogenesis and effectively block bone resorption. There are side effects of these antiresorptive drugs but they are not commonly seen. Hypocalcemia, which should be a consequence of inhibition of bone resorption, is not an issue. There is about a 1% incidence of subtrochanteric femoral fractures with the bisphosphonates as well as osteonecrosis of the jaw that appears to be limited to cancer patients or those having extensive dental work. More commonly, gastroesophageal reflux symptoms can be seen in those taking oral bisphosphonates.

The anabolic drug available is parathyroid hormone (PTH). It is given subcutaneously on a daily basis for 1 to 2 years. It results in gain in bone density, especially in the lumbar spine but also to a lesser extent in the hip. Fracture incidence appears to be reduced. The use of PTH is restricted to adults because rats developed an increased incidence of osteogenic sarcoma, a disease that strikes mainly those with open epiphyses, namely, children and young adolescents. Even though the drug is being safely used off label as hormone replacement in children and adolescents with hypoparathyroidism, the FDA placed a black box warning on the drug label prohibiting its use in children. A newer agent, a monoclonal antibody against the osteocyte product sclerostin, an inhibitor of the anabolic Wnt signaling pathway that promotes osteoblastogenesis, appears to be promising in clinical trials and may have promise of safe use in children with chronic bone loss. PTH in fact appears to achieve its anabolic effect by inhibiting sclerostin production in the presence of CD8+ peripheral blood mononuclear cells. The objective of these bone agents is to prevent bone breakdown and stimulate new bone formation, thus creating stronger bone and reducing risk for fracture.

THE BONE HEALTH CLINIC

Given all this information, how is it applied in a bone health clinic? Ideally, any patient of any age who suffers a fragility fracture, anyone over the age of 70, those with a chronic inflammatory disease, and women who are postmenopausal would all receive an evaluation of bone health and appropriate treatment if indicated. Initial evaluation consists of bone density testing and blood work for concentrations of calcium, phosphorus, magnesium, PTH, and 25-hydroxyvitamin D. If warranted, lateral vertebral X-rays to detect compression fractures are done as are determinations of blood or urine biomarkers of bone resorption and blood biomarkers of bone formation. The efficacy of this screening procedure and placement as indicated on a therapeutic course of an appropriate anti-resorptive or anabolic agent has been demonstrated in one program, Kaiser Permanente Southern California, in which it reduced expected hip fractures per year by as much as 40%. Therefore, given personnel with relevant expertise, a bone health program can be a useful adjunct to an orthopedic surgery service by providing early screening and evaluation of bone quality as needed. Pharmacotherapy will be prescribed as indicated with the end point being the improvement of bone mass and quality of life for our patients.

REFERENCE

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RECOMMENDED READING

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DISCLOSURE

The author sat on the Bone Toxicity Advisory Board of Novartis Pharmaceuticals in 2012.