EDITORIAL

OLD BONES

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Bone is a dynamic organ in which osteoblasts, under inhibitory control of sclerostin, creates new bone osteoblasts by releasing RANK-L to activate osteoclasts to remove bone. This dynamic network is under local control of miRNAs and long noncoding RNAs to balance the effect of bone stressors on bone formation (1).

With aging there is an increase in fragility fractures. Fractures are a more common reason for older persons requiring interaction with medical professionals than any other disease and are one of the higher components of annual hospital costs (2). Over 20% of older persons with hip fractures die within a year and they are a major cause of disability (3). Vertebral fractures are a major cause of back pain, loss of height, reduced pulmonary function, dysphagia, deformity and a decline in quality of life.

The need for collaboration between orthopedic surgeons and geriatricians to improve outcomes of older persons with fractures led to the forming of the first geriatric orthopaedic unit by Bobby Irvine and Michael Devas in 1963 (4). The motto of this unit was “Bedrest is rehabilitation for the grave.” Richard Lefroy published the first positive effects of a geriatric orthopedic unit in Perth, Australia (5). A meta-analysis found that these combined programs resulted in a decrease in both in-hospital and long-term mortality (6). Two recent approaches improving hip fracture care are: (i) providing regional nerve blocks on arrival at hospital to reduce pain and improve function outcomes (7) and (ii) injection of a triphasic calcium based implant (AGN-1) into the contralateral proximal femur to reduce subsequent hip fracture in the other hip (8).

There are three major bone diseases in older persons – Paget’s disease of bone, osteomalacia, and osteoporosis.

Paget’s Disease of Bone

Paget’s disease is a bone disease in which rapid destruction by osteocytes is imbalanced with excess osteoblastic reformation. It is more common in males of 55 years of age. Over the last 30 years, it has decreased from 4-5% to 1 to 2% (9). While the reason for this decrease is uncertain it is suggested that it is due to vaccination for the paramyxovirus measles (10).

Paget’s disease results in bone pain and deformity, fractures,

deafness and high output heart failure. If there are characteristic findings on x-rays an increased alkaline phosphatase can help confirm the diagnosis. Treatment is with intravenous infusion of the long acting biophosphonates, zoledronic acid.

Osteomalacia

Osteomalacia is weak bones that break easily because of less mineralization resulting in the bone breaking down at a greater rate than it forms. The major cause is vitamin D deficiency. Other causes are celiac disease, antiviral and antiepileptic drugs, intestinal bypass, kidney or liver disease (11).

The signs and symptoms of osteomalacia include dull bone pain, muscle pain and weakness, Looser’s fractures, numbness and muscle twitching and a prolonged QT on ECG. Blood tests are a low calcium and phosphate and elevated alkaline phosphatase and parathormone levels. Diagnostic is low bioavailable 25(OH) vitamin D. Total vitamin D levels are variable depending on the color of the skin and as such are no longer recommended (12, 13). Treatment is replacement with about 1,000 IU of vitamin D daily.

Osteoporosis

Osteoporosis is a decrease in bone mineralization in older persons leading to weakness of bones and subsequent fracture. Osteoporosis is dependent on the size of bones built during childhood. It is related to a number of genetic factors especially RANK/RANK ligand/osteoprogenin, WNT and estrogen receptor 1 (14). Osteoporosis is often not recognized nor treated by physicians. For this reason, screening is recommended in all women between 50 to 60 years of age and males over 70 years of age. Screening is done utilizing the FRAX (WHO Fracture Risk Assessment: www.shef.ac.uk/FRAX). Risk factors for osteoporosis can be remembered by the mnemonic OSTEOPOROSIS (Table 1) together with diseases such as diabetes mellitus and COPD. If risk factors are present bone mineral density (BMD) should be measured using a dual energy x-ray absorptiometry (DEXA) scan. Rate of bone loss is important to detect persons at risk for developing osteoporosis. The DEXA should be repeated every 2 years, but because of seasonal fluctuations in bone calcification it should be done in

the same month. In persons with diabetes mellitus, the DEXA often shows high mineralization but the bones have weak structure. Ultrasound of the tibia is an alternative approach. A recent approach to screening and management has been developed (Figure 1) (15).

Table 1

Risk Factors for Osteoporosis: The Osteoporosis Mnemonic

L ow calcium intake
S eizure medications
T hin build/weight loss
E thanol
H yp O gonadin
P rior fractures
T hyr O id excess
R ace
O ther relatives
S teroids
I nactivity
S moking

Figure 1

Hypothetical approach to screening and treating osteoporosis in women. In general treatment should be driven by FRAX score

Persons with osteoporosis need adequate daily calcium intake, which is about 1g a day. Higher total calcium intake leads to increased cardiovascular disease and mortality (16). The average female ingests 600 mg per day and males about 800 mg per day. If calcium is to be replaced it needs to be given at night (as calcium comes off bone while lying in bed). It can best be replaced with one 8 oz low fat yogurt.

In persons with a white skin the normal value of 25(OH) vitamin D is 20 to 25 ng/ml (50 – 75 nmol/L) (17). In dark skinned persons there is a reduction in vitamin D binding protein and in these individuals bioavailable 25(OH) vitamin D should be measured. There is no need to replace vitamin D at

more than 1000 IU/day.

Drugs for Osteoporosis

Estrogen is needed for all women with premature menopause or with menopausal symptoms (18). In general, it is not recommended that estrogen be taken for more than 5 years. It decreases hip fracture. Raloxifene increases bone mineral density, reduces spine fractures and a 65% reduction in breast cancer (19).

Alendronate, a bisphosphonate, enhances bone mineral density and decreases hip fractures (20). Its main side effects are esophagitis, uveitis, esophageal cancer, osteonecrosis of the jaw and atypical femoral diaphyseal fractures. It needs to be recognized that alendronate decreases hip fractures to a much greater extent than it causes atypical fractures (21). For persons who cannot take alendronate orally, intravenous zoledronic acid is recommended (22).

Denosumab is a human monoclonal antibody that blocks RANK ligand (23). Denosumab is given by subcutaneous injection every 6 months. It has a similar effectiveness to bisphosphonates and the same side effects. In addition, it causes skin infections, such as cellulitis. It is much more expensive than bisphosphonates.

Two parathormone analogs, teriparatide and abaloparatide are available for persons with severe osteoporosis (T score <-3.0) or severe hip fractures (24-26). They are anabolic agents which are recommended not to be taken for longer than 2 years: A number of different delivery mechanisms (e.g., nasal, patch, microchips) are available for teriparatide.

Sclerostin is an antagonist of the Wnt/ β -catenin signaling pathway. An antibody to sclerostin, romosozumab, is available as an anabolic agent which markedly increases bone mineral density and decreases vertebral fractures (27). Its use should be limited to 12 months. It causes ectopic calcification and it can cause myocardial infarction. It also causes arthralgia.

Testosterone increases bone mineral density in men but there have been no large controlled studies to show that it prevents hip fracture (28). In addition, to improving BMD it increases bone strength (29).

Conclusion

Diseases of old bone result in an increase in hip fracture. These bone diseases are often under-recognized and undertreated by physicians in older persons. Table 2 provides approximate prices of drugs for osteoporosis. Physicians should take these costs into account when choosing treatments.

In persons at risk for hip fracture, besides strengthening the bones it is essential that physicians pay attention to fall risk. The Toulouse-St. Louis University MiniFalls test should be used (30) along with the F3ALLS treatment paradigm (31). In addition, all persons at risk for fracture should be screened for frailty – using the FRAIL – and treated with the frail algorithm

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(32-36). In addition, sarcopenia should be screened for using the SARC-F and if present, be appropriately managed (37-39).

Table 2
Cost of Medications for Osteoporosis in the USA

Medication	Cost/Year
Vitamin D	\$72
Alendronate	\$120
Zoledronic acid	\$1,173
Denosumab	\$1,650
Teriparatide	\$6,700
Romosozumab	\$21,900

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