An Update on Osteoporosis

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Osteoporosis is being increasingly recognized as a common condition associated with significant morbidity and mortality. Hip fractures are associated with a 20% mortality by 12 months after the event in women and approximately 40% mortality in men. Vertebral fractures have a similar mortality rate by five years post event. Men are less likely than women to be diagnosed with osteoporosis or receive adequate therapy.

Osteoporosis Canada has developed guidelines identifying absolute fracture risk by age and BMD. Absolute fracture risk is further modified by use of glucocorticoids in doses of 7.5 mg for three months or longer as well as the presence of a fragility fracture which places the individual at the highest risk of fracture. Ten year absolute fracture risk is categorized into low (< 10%), moderate (10% to 20%) and high risk of fracture (> 20%). These guidelines will enable physicians to determine which patients are at high risk of fracture and appropriately target individuals for pharmacologic intervention.

Evaluation

Evaluation requires a detailed history and physical with identification of factors which can contribute to osteoporosis and exclude secondary causes of bone loss. Height should be measured at baseline and at serial assessment. Height loss can reflect underlying vertebral compression fractures. Individuals with back pain or height loss or dorsal kyphosis should have lateral spinal x-rays in order to detect the presence of vertebral fracture or additional skeletal pathology.

Common secondary causes of bone loss include:

- Hyperparathyroidism (primary or secondary)
- Vitamin D insufficiency
- Malabsorption
- Hypercalciuria
- Hyperthyroidism
- Chronic lung disease
- Malignancy
- Rheumatoid arthritis
- Hepatic insufficiency

Following evaluation and exclusion of secondary causes of osteoporosis, therapy is indicated. Lifestyle changes are recommended with restriction of alcohol to less than two drinks a day, smoking cessation and reduction of salt intake. A daily weight-bearing exercise program is also emphasized. Calcium intake should be adequate with the total daily intake from diet and supplements being 1,200 mg q.d. of elemental calcium.

Therapy

Antiresorptive therapy is effective in normalizing bone remodelling. With estrogen deficiency, osteoclast activity is significantly increased and this is lowered into the premenopausal range with inhibition of the osteoclast. Nitrogen-containing bisphosphonates, namely alendronate, risedronate and zoledronate, are effective in reducing the rate of remodelling and improving bone density and reduce the risk of vertebral and non-vertebral fracture by approximately half. Nitrogen-containing bisphosphonates are poorly absorbed orally and must be taken on a fasting basis half an hour before breakfast. In ideal conditions, < 5% of the bisphosphonate is absorbed. The generic preparations may not have the same esophageal transit time and absorption and this can impact effect on remodelling, bone density and fracture risk. IV zoledronate is a valuable option particularly for those unable to take oral bisphosphonates or who are not compliant with weekly or monthly administration.

Raloxifene is a valuable antiresorptive agent. It is effective in reducing vertebral fracture risk but has not been shown to reduce the risk of non-vertebral fractures or hip fractures. It is effective in reducing the risk of breast cancer. It can be given in combination with a nitrogen-containing bisphosphonate.

Hip fractures are associated with a 20% mortality by 12 months after the event in women and approximately 40% mortality in men.

Anabolic therapy remains a powerful treatment option for those who have failed antiresorptive therapy. Teriparatide is the only anabolic agent available in Canada and is effective in improving new bone formation and reducing the risk of vertebral and non-vertebral fractures. It improves microarchitecture and impacts both bone quantity and quality.

Denosumab is a new antiresorptive agent expected for release in Canada in 2010. Denosumab is a fully human monoclonal antibody which binds to receptor activator of nuclear factor kappa β (RANK) ligand and prevents osteoclast formation, function and survival and is effective in normalizing bone remodelling. Significant reductions in fracture have been noted with decreases in vertebral, non-vertebral and hip fracture. The drug is administered subcutaneously twice a year and is not renally excreted.

Osteonecrosis of the jaw (ONJ)

ONJ has been linked to high-dose bisphosphonate use in cancer patients and occurs in up to 10% of cancer patients most commonly after dental surgery such as a tooth extraction. A causal relationship between low dose oral or IV bisphosphonates and ONJ as used in osteoporosis patients has not been identified.

Multiple factors have been implicated in the development of ONJ. The exact mechanism by which high-dose bisphosphonates increase the

risk of ONJ is not fully understood. It may be due to local trauma with inadequate clearance of necrotic debris in the presence of impaired osteoclast function. Secondary infection may contribute to the development of local osteonecrosis; as well, bisphosphonates may have toxic effects on local soft tissue and impair the function of epithelial and vascular cells and prevent healing of the surgical site.

Canadian guidelines recommend that bisphosphonates be stopped prior to dental surgery and can be resumed following healing of the surgical site. Canadian recommendations also emphasized the importance of maintaining good oral hygiene and semiannual dental assessments.

Drugs affecting skeletal health

Thiazolidinediones (TZD) increase insulin sensitivity, however, they inhibit osteoblast differentiation from mesenchymal stem cells and promote adipocyte differentiation while suppressing osteoblast formation. TZDs, both rosiglitazone and pioglitazone, have been associated with an increased risk of non-vertebral fracture. Individuals who have osteoporosis and are experiencing fractures should take alternative oral hypoglycemic agents.

PPIs and H2 blockers increase gastric pH and decrease calcium absorption. Individuals should be switched to calcium citrate or take calcium carbonate with meals.

Selective serotonin reuptake inhibitors (SSRIs) have been associated with increased bone loss in older men and women. SSRI use has been associated with an increased risk of fracture as noted in men and women > 50-years-old. As serotonin receptors are present on bone cells and gut serotonin inhibits osteoblast proliferation and bone formation, it may be appropriate to review the use of SSRIs in those with fragility fracture.

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Atypical fractures

Atypical subtrochanteric fractures have been reported before the availability of nitrogen-containing bisphosphonates. There have been growing reports of atypical femoral fractures occurring with little or no trauma and concern regarding a possible link between these fractures and bisphosphonate use has been raised. There was, however, no evidence of an increased risk of these fractures with bisphosphonate use in a recent study evaluating approximately 76,000 men. In this population,

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the risk of subtrochanteric fracture was approximately 1.2 per thousand and the risk appears to be very small, if at all present.

New research is focusing on developing molecules which will serve as anabolic agents. Sclerostin is secreted by osteocytes and can suppress Wnt signaling and decrease bone formation. An anti-sclerostin antibody would function as a potent anabolic agent and is currently being evaluated.

In summary, effective therapies are currently available. It is important to identify those at risk and initiate appropriate therapy. Dx

Resources
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