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New Drug Developments of Osteometabolic Disorders Examining the Relationship Between Metabolic Disorders

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Abstract

Osteoporosis is the most common contributing factor of spinal fractures, which characteristically are not generally known to produce spinal cord compression symptoms. Recently, an increasing number of medical reports have implicated osteoporotic fractures as a cause ofserious neurological deficit and painful disabling spinal deformities. This has been corroborated by the present authors as well.

Keywords: Osteoporosis; fractures; myelopathy; deformity; paget's disease; back pain; spinal stenosis

Introduction

Osteoporosis is characterized by skeletal fragility and susceptibility to fracture attributed to reduction of bone mass and deterioration of bone micro-architecture. It is a metabolic bone disease occurring in both men and women, particularly when they grow older. Osteoporosis is a major health problem due to the high morbidity, mortality, and significant health care cost involved. Osteoporosis affects more than 200 million people globally. Osteoporosis causes 1.3 million fractures, with 500,000 vertebral, 250,000 hip, and 240,000 wrist fractures costing $10 billion per annum in the USA.

Pathophysiology of osteoporosis

An imbalance between osteoclast-mediated bone resorption and bone formation remains a key means to understanding and treating postmenopausal osteoporosis. The RANK-L/RANK/OPG pathway mediates the production and activity of cells in the osteoclast lineage. RANK-L, a member of the TNF superfamily, is produced by bone marrow stromal cells and lining cells both of the osteoblastic lineage. It interacts with RANK, a TNF receptor family member, on cells of the macrophage/monocyte lineage as well as mature osteoclasts. The soluble protein OPG, released by osteoblasts into the microenvironment, interrupts the interaction between RANK-L and RANK in the role of OPG as a decoy receptor. Knockout and transgenic mouse models, as well as rare cases of human mutations in the genes encoding the members of this pathway, further establish the essential features of this paradigm for the control of osteoclastogenesis and bone resorption.

Therapies for osteoporosis

Antiresorptive agents: bisphosphonates

Ibandronate.

This potent aminobisphosphonate has been studied in a variety of dosing regimens. In a study called the MOBILE (Monthly Oral Ibandronate in Ladies) trial, responses in bone mineral density (BMD) and bone turnover markers in postmenopausal women with low bone mass were compared on daily and monthly dosing schedules. The analysis of responses after 1 yr of treatment showed noninferiority for the three-monthly regimens and superiority in the responses in the cohort of women dosed at monthly (150 mg) compared with daily (2.5 mg) schedules.

The two most recent trials noted above (MOBILE and DIVA) supported the approval of ibandronate as a 150-mg tablet for monthly use and a 3-mg iv preparation for the treatment of postmenopausal osteoporosis.

Alendronate

The Fracture Intervention Trial (FIT) established the efficacy of alendronate in the prevention of fractures in postmenopausal osteoporosis nearly a decade ago. FIT included approximately 4–5 yr of treatment with alendronate or placebo. Subsequently, women who had been treated with alendronate for 3–4.5 yr were randomized to either daily alendronate or placebo for an additional 5 yr in FLEX (the FIT Long-term Extension) . BMD, biochemical markers of bone turnover, and fractures were assessed in FLEX.

Risedronate

Risedronate has been FDA-approved for treatment of osteoporosis in men. Recent data from a 1-yr open-label study of men with primary or secondary osteoporosis showed increases in BMD at the lumbar spine, femoral neck, and total hip that were significantly greater than placebo and a 60% reduction in new vertebral fractures *vs.* the control group.

Antiresorptive therapy: selective estrogen response modulators

Several studies assessing the advantages and or disadvantages of SERM therapy on other than skeletal endpoints in postmenopausal women have recently been published. In 2004, the CORE (Continuing Outcomes Relevant to Evista) trial reported that postmenopausal women treated with raloxifene for 8 yr demonstrated a 66% reduction in the risk of invasive breast cancer compared with placebo.

Anabolic and combination therapies

Teriparatide and alendronate.

As important as it is to develop new therapies and identify novel drug targets to stave off bone loss, it is equally important to maximize the use of approved therapies in combination or in sequence—especially if these therapies have different mechanisms of action. For this reason, there is inherent appeal to combining a powerful anabolic agent such as PTH either the 1–84 or 1–34 form of the hormone—with an antiresorptive agent such as alendronate. The results of this strategy were reported in two studies in 2003 one in women and the other in men with osteoporosis. Adding alendronate to therapy with PTH, in both men and women, blunted the anabolic effects of PTH both in terms of BMD and bone formation marker responses.

Conclusion

A novel treatment has been established for obesity and osteoporosis by targeting apoptotic pathways of adipocytes. Leptin treatment in leptin-deficient (*ob*/*ob*) mice suppressed food intake, reduced body weight, lowered body fat levels, increased energy expenditure, induced adipocyte apoptosis, and increased BMD and bone formation. Additionally, lipid-lowering treatment reduced osteoporosis. Statins, a lipid-lowering medication helps to reduce serum cholesterol, has been reported to increase BMD in postmenopausal women. Several criteria also have to be taken into consideration for management of osteoporosis in diabetic patient. Examples include avoidance of thiazolidenediones (TZDs), exerting good glycemic control, as well as taking calcium and vitamin D supplementation. Researchers have also reported denosumab (a FDA-approved osteoporotic drug) increased human pancreatic beta cells proliferation. Meanwhile, animal studies showed that treatment of hypertensive mice with an angiotensin-converting enzyme (ACE) inhibitor (e.g., enalapril) improved osteoporosis and hypertension. Therefore, in our opinion, the curtailment of MetS progression may help in preventing bone loss. However, there are still no drugs available that can halt both diseases.

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