Diagnostics, Therapeutics, and Health Informatics in Osteoporosis

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INTRODUCTION

Osteoporosis, usually silent until a fracture occurs, is among the most common health problems facing elders worldwide. By definition, osteoporosis is a "systemic" skeletal disease characterized by a low bone mass and a micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture ("*The Burden of Musculoskeletal Conditions,*" 2003). The incidence of osteoporotic hip fracture increases exponentially with age, and the increase in older persons globally could dramatically increase the number of hip fractures, posing a devastating increase in disability and cost for elders worldwide. Therefore, it is imperative that diagnostic and treatment measures be developed and instituted worldwide to support preventative measures for osteoporosis and consequential fractures. Toward that purpose, the World Health Organization (WHO) has declared 2002–2011 as the *Decade of the Bone and Joint*, uniting nations throughout the world in the commitment of energy and resources to accelerate progress in bone health and prevention of fractures. Keeping in mind this global context, this discussion includes information about the prevalence and impact of osteoporosis, its signature pathology (including bone remodeling), factors which place individuals at risk for developing osteoporosis, and the role of diagnostics, therapeutics, and informatics in the realm of osteoporosis. Encouraging information is also provided about recent innovative technological developments that may enhance our ability to detect and treat osteoporosis earlier, in time to reduce and better manage its unwelcome sequelae.

PREVALENCE AND IMPACT

The WHO estimates that up to 70% of women older than 80 years of age have osteoporosis ("*The Burden of Musculoskeletal Conditions,*" 2003). One in every two women and one in every five men over 50 years of age experience an osteoporotic fracture during their lives, and more women die from the after-effects of osteoporotic fractures than from cancer of the ovaries, cervix, and uterus together. There are 1.5 million osteoporotic fractures in the U.S. each year, 20% hip fractures, 50% vertebral fractures that lead to height loss, and 30% at the wrist and other sites. One fourth (25%) of all postmenopausal women will develop a vertebral deformity and another 15% will sustain a fractured hip, numbers that could triple by 2040 ("*Bone Health and Osteoporosis: A Report,*" 2004).

Hip fractures are the most severe consequence of osteoporosis, and are associated with lengthy hospital admissions, difficulty in performing activities of daily life, nursing home placement, and a high rate of mortality. The annual worldwide incidence of hip fracture is projected to grow to 2.6 million by 2025 and to 4.5 million by 2050. Virtually all persons in the U.S. with hip fractures are hospitalized, and 25% of those who sustain hip fractures require long-term nursing home care. Spine fractures are considerably less problematic in terms of cost, with only 10% requiring hospitalization and less than 2% being admitted to a nursing home. However, they account for 66,000 physician office visits and at least 45,000 hospital admissions each year.

The economic burden of osteoporosis to society is immense. Each year in the U.S., osteoporotic fractures

result in more than 500,000 hospitalizations, 800,000 emergency room visits, more than 2.6 million physician office visits, and the placement of nearly 180,000 individuals in nursing homes. It is estimated that each hip fracture represents approximately $40,000 in total medical costs. Care to white women comprises the majority of these costs, but men and nonwhite women of all ages account for $1 billion in direct costs of osteoporotic fractures. Due to the late age at which the expenses related to care occur, osteoporosis accounts for 14% of all nursing home days. Given that 75% of all hip, spine, and distal forearm fractures occur in persons 65 years and older, the direct costs are largely borne by society, in the form of social reimbursement programs. In the United States, Medicare pays approximately one half of these costs, and Medicaid covers an additional one-fourth of the expense.

But the impact of osteoporosis on the personal lives of the patients and their families is even greater. Nearly one in five persons who sustain a hip fracture end up in a nursing home, and about 20% will die before a year has passed. Two-thirds of hip fracture patients never return to their prefracture level of function, and many lose their ability to walk. More than one-third (37%) lose their ability to dress themselves, 58% lose their ability to move from their chair to standing, and 60% lose their capacity to walk across the room. Approximately half of the individuals who sustain hip fractures never walk independently again, even if they were ambulatory before their fracture (Gueldner, Burke, Wright, & Newman, 2007).

PATHOLOGY

Osteoporosis is not only the result of accelerated bone loss during aging, but may also develop because of suboptimal bone growth in childhood and adolescence, or by the use of certain medications (most notably steroids) for the treatment of other health problems. Fracture risk is currently estimated by measuring bone mineral density (BMD), with the risk of fracture increasing sharply as BMD declines. The estimated life-time risk for wrist, hip, and vertebral fractures is 15%. Hip fracture rate is used to calculate the osteoporosis fracture burden. Prior fracture is one of the most important predictors of future fracture. The risk of hip fracture after a wrist fracture increases 1.4-fold in U.S. women, 1.5-fold in Swedish women, and 1.8-fold in Danish women. Wrist

fracture is an even stronger predictor of hip fracture in men; U.S. men who had a wrist fracture were found to be 2.3 times more likely to sustain a hip fracture, and Swedish men with wrist fracture were 2.8 times more likely to sustain hip fracture.

Although an individual's height and unique bone structure are developed by late adolescence, new bone continuously replaces old bone throughout life in a process referred to as bone remodeling. Through the remodeling process, approximately 10% of the skeleton is replaced each year, with most of the adult skeleton being replaced every 10 years. The skeleton consists of 80% cortical (compact) bone, which is located predominately on the outer surfaces of the bone, and the remaining 20% is inner trabecular (spongy) tissue, which forms a large portion of the vertebrae, proximal femur, and distal radius. If less new bone is formed during the remodeling process than the amount of old bone removed, a net loss of bone occurs, and the resulting fragile bone is more likely to break with less trauma, as is the clinical problem with osteoporosis. Remodeling occurs in both types of bone, but most (80%) occurs in the trabecular bone. Thus fractures in regions of high trabecular area such as the hip, spine, and wrist are more likely to occur.

In the complex bone remodeling sequence, bone cells lie quiescent until osteoclasts (bone resorbing cells) are stimulated to resorb (remove) a small volume of bone. While some details of the actual remodeling process remain unclear, it is thought that this resorbing activity is increased by a number of factors, including parathyroid hormone (PTH) and thyroxine, and that it is decreased by estrogen, testosterone, vitamin D, calcium, high phosphorus levels, and sometimes by cytokines from osteoblasts (bone forming cells). Localized prostaglandins and interleukins may also exert a stimulatory or inhibitory effect on this remodeling process. A low calcium intake stimulates the secretion of PTH, which in turn activates the osteoclasts to release lysosomal enzymes which digest bone matrix, causing the release of calcium and other bone minerals and proteins. After the resorption cavity is formed, a cement line is laid down by macrophage-type mononuclear cells, limiting further resorption of bone in that particular area. The cement line is rich in osteopontin, which may serve to shut off osteoclast (resorption) activity and stimulate osteoblast (rebuilding) activity. A growing number of pharmaceutical modalities have been developed with the goal of reducing bone loss or

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