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Osteoporosis: risk factors and diagnostic approach

Kuchuk-Synyavskyy, N.O.

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Chapter 1

General introduction

Osteoporosis is one of the serious diseases facing the ageing population. Osteoporosis is defined as a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue (1).

The resulting increase in bone fragility increases the risk of fractures, which represent the major clinical consequences of the disease and lead to pain, decrease of physical and social functioning and to loss of quality of life (2). Common sites for osteoporotic fracture are the spine, hip, distal forearm and proximal humerus. Hip fractures cause acute pain and loss of function, and nearly always lead to hospitalization, with slow recovery and often incomplete rehabilitation. Vertebral fractures may occur either without serious symptoms, or with severe pain and disability. They often recur, and the consequent disability increases with the number of fractures. Distal radial fractures also lead to pain and loss of function, but functional recovery is usually good or excellent (3). Osteoporosis is defined according to the World Health Organization as a bone mineral density (BMD) in the spine and/or proximal femur 2.5 or more standard deviations below normal peak bone mass (T-score ≤ -2.5). The term *established osteoporosis* is used when one or more fragility fractures have occurred, in addition to a BMD T-score ≤ -2.5 (4). A problem is that many fragility fractures (about 50 %) occur with a BMD > -2.5 , implicating that -2.5 is not a sharp fracture threshold.

Pathogenesis of osteoporosis and fractures

Bone is a dynamic tissue composed of living cells (osteocytes) embedded in the intercellular matrix. The bone matrix is reinforced with collagen fibers and is heavily calcified. Bone matrix can withstand bending, twisting, compression, and stretch. Besides being hard owing to insoluble calcium salts, it is highly resistant to tensile stress because of an abundance of collagen fibrils, mostly type I (5). Bone serves several important functions in the body: locomotion, protection against trauma, and provision of a calcium reservoir. Throughout life, bone is constantly resorbed and formed in the process known as remodeling. Osteoblasts are the cells responsible for the formation and mineralization of bone, and osteoclasts for bone resorption. During growth, bone formation exceeds bone resorption, and the peak bone mass is reached between ages 20 and 30 years. Thereafter similar rates of formation and resorption stabilize the bone mass until age 35 to 40 years, at which time resorption begins to exceed formation, and the total bone mass slowly decreases (6).

Pathogenetic factors favoring the osteoporotic process are those impairing the accumulation of bone during growth and those accelerating the loss of bone during later life.

According to an unitary model for the pathophysiology of involutional osteoporosis, proposed by Riggs et al in 1998, estrogen deficiency was identified as the major cause of both the early, accelerated, and late, slow phases of bone loss in postmenopausal women and as a contributing cause of bone loss in older men (7). After the menopause, estrogen deficiency leads to an increase in bone turnover with an imbalance between bone formation and resorption. The pathophysiological mechanism involves the release of cytokines in the bone marrow environment, such as tumour necrosis factors and interleukins, which stimulate osteoclastic bone resorption. In aging men, loss of bone seems to be associated with low bone formation rather than high bone resorption, and that may be related to declining androgen and estrogen levels.

It has been established that estrogen replacement at or after menopause, whether natural or induced, prevents postmenopausal bone loss and results in an increase in bone mineral density. Furthermore, even in postmenopausal women, the small amounts of estrogen produced endogenously are determinants both of bone mineral density and fracture risk (8).

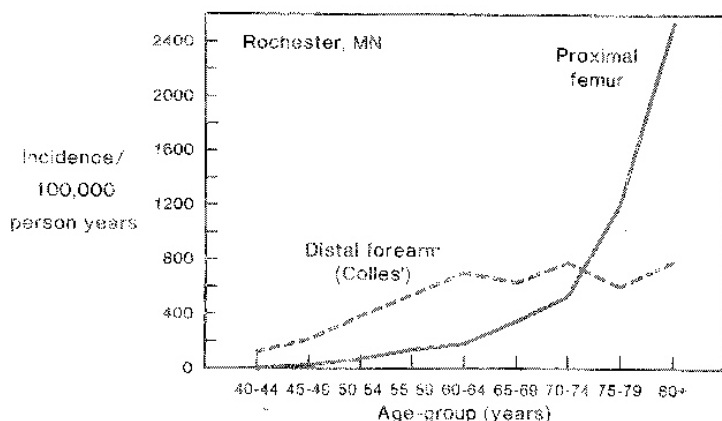
Age-related changes in the pattern of fractures have been noted with regard to sex distribution and to the frequency of occurrence and the location of the fracture. Among women, the incidence of either vertebral fractures or Colles' fractures of the distal forearm early after menopause is five times greater than the incidence of hip fractures, while the incidence of hip fractures initially is low but rises exponentially (Figure 1) (9). Therefore, vertebral and Colles' fractures, that exhibit early postmenopausal increase, and occur at sites that contain predominantly trabecular bone, were designated earlier by Riggs as type A fractures, associated with type I osteoporosis (estrogen-deficiency in postmenopausal women). Fractures of the hip, proximal humerus, proximal tibia, and pelvis, share the similar pattern of occurrence, in sites that contain both cortical and trabecular bone, and were designated as type B fractures, associated with type II osteoporosis. For type II osteoporosis, there may be two major causes - impaired bone formation, and secondary hyperparathyroidism.

Other endocrine diseases such as primary hyperparathyroidism, hyperthyroidism and hypercortisolism also can induce bone loss. Furthermore, bone loss may be accelerated in the elderly by low calcium intake and/or poor vitamin D status due to inadequate sunlight exposure and a low dietary intake. Secondary hyperparathyroidism, however, has been proposed as the principal mechanism

whereby vitamin D deficiency, being an important cause, could contribute to the pathogenesis of hip fractures (10). Age-related increase in parathyroid function is related to the age-related decrease in calcium absorption, and may be caused by impaired metabolism of 25(OH)D to 1,25(OH)₂D. Although vitamin D deficiency is common in older people and in patients with osteoporosis (11), the required serum 25(OH)D for adequate bone health is still debated. Despite the growing evidence from the international literature about high prevalence of unrecognized vitamin D deficiency worldwide, there is still no consensus on a cut-off value for the definition of deficient or insufficient vitamin D status as well as a definition for an adequate vitamin D status.

Therefore, according to Riggs et al (9), involutional osteoporosis can be divided into two distinct syndromes that differ with respect to epidemiology, patterns of trabecular and cortical bone loss, parathyroid function, and cause.

Figure 1. Difference in patterns of type A and type B fractures is illustrated by incidence of Colles' fracture and hip fracture, respectively, among women residing in Rochester, Minnesota.



Adapted with permission from (9) Riggs BL, Melton LJ, III 1983 Evidence for two distinct syndromes of involutional osteoporosis. *Am J Med* 75:899-901.

Case-finding in osteoporosis

Osteoporosis is often diagnosed at the stage where fractures have already occurred. The diagnosis is usually based on risk factors followed by bone densitometry, referred to as a case-finding approach. Important clinical risk factors include a fracture after the age of 50 years, prevalent vertebral fracture, previous fragility fracture, low body weight, parental history of hip fracture,

glucocorticoid treatment (>7.5 mg prednisolone daily or equivalent for 3 months or more), severe immobility. Different approaches have been recommended worldwide, using a combination of clinical risk factors with or without BMD measurement (12), to identify patients with osteoporosis. The Dutch Osteoporosis Guidelines, for example, identify a fracture in a woman above the age of 50 years as one of the most important risk factors for future fracture which should lead to bone mineral density (BMD) assessment (13).

Since the publication of the results of the fracture liaison service in Glasgow (a program for the evaluation and management of patients with osteoporotic fracture) (14), several fracture and osteoporosis (FO) clinics emerged in The Netherlands to improve the identification of patients with osteoporosis and to make recommendations for treatment (15-17).

Although the results are positive, little data is available about non-responders and the compliance of participating patients. It is well known that only half of the patients comply with long-term therapy, and that poor adherence to treatment is common in osteopenia and osteoporosis, even when associated with fractures (18). Therefore, the analysis of adherence of patients to advice and their persistence to treatment will provide new insights in how to increase adherence and persistence in patients with osteoporosis and to ensure better protection against future fractures.

OUTLINE OF THE THESIS

In **Chapter 2**, the relationship between estrogen and androgen status and various parameters of bone quality in older men and women, such as QUS, BMD, bone turnover markers, bone loss and osteoporotic fractures, is described. This study was performed within the framework of the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in the ageing population in the Netherlands. **Chapter 3** discusses the results of a global study on vitamin D status according to season in postmenopausal women with osteoporosis, in different countries with different economic status all over the world using a central laboratory facility, investigating the relationship between serum 25(OH)D and parathyroid function, bone turnover markers and bone mineral density (BMD). In **Chapter 4**, we describe a study on the estimation of the threshold serum 25(OH)D with regard to serum PTH, bone turnover markers, bone mineral density, bone ultrasound parameters and physical performance in LASA, a population-based study. **Chapter 5** describes an implementation study on

a case-finding strategy for osteoporosis in patients with a recent fracture diagnosed at the Department of Trauma Surgery according to the Dutch Osteoporosis Guidelines. This study investigated the additive value of Vertebral Fracture Assessment (VFA) as a tool for diagnosing prevalent vertebral fractures, in this case-finding approach. The evaluation of the acceptance of above-mentioned strategy both by the patients and their general practitioners is discussed in **Chapter 6**, which provides information on compliance, described in terms of adherence and persistence for participating patients, as well as the concordance of the general practitioners (GPs) with our advice. We used terms “persistence” (or continuation rate), to describe the percentage of patients still on treatment at the end of the period of interest, and “adherence” to describe whether patients followed our advice or not.

Chapter 7 summarizes and discusses the main findings of the studies described in this thesis. Finally, the possible implications of the findings for future research and clinical practice are considered. A flowchart for the diagnostics and treatment advice in osteoporosis is proposed in Appendix.

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