J Musculoskel Neuron Interact 2003; 3(3):189-193

Original Article

Hylonome

Relevance of bone mineral density, bone quality and falls in reduction of vertebral and non-vertebral fractures

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Abstract

All epidemiological studies conclude that without prompt, concerted and well-designed prevention programs, the increasing cost related to osteoporotic fractures will become an unbearable burden for the community within the next fifteen years. However, the most effective way of setting up such preventive strategies is not yet unequivocally defined. Low bone mass and microarchitectural damage of bone tissue may account for a large part of the epidemiology of vertebral fractures. Extraskeletal determinants, including low muscle strength, poor balance and gait, all resulting in an increased propensity to fall, also play a major role in the occurrence of hip fracture. Depending on the localization of the fractures, the relative importance of skeletal and extraskeletal risk factors can significantly differ. For prevention of vertebral fractures, drugs affecting bone mass and skeletal architecture may provide a substantial benefit while hip fracture prevention will be more successfully targeted by multi-faceted strategies concentrating not only on the skeletal dimension of the fracture but also aiming, either pharmacologically or through multi-intervention programs, at a reduction in the incidence and in the consequences of falls in the elderly.

Keywords: Osteoporosis, Prevention, Falls, Bone Mineral Density, Bone Quality, D-Hormones

Introduction

Osteoporosis-related fractures, mainly at the spine and hip, are considered a major medical, social and financial burden in most developed countries[1]. Both spinal and femoral fractures have consistently been linked to a severe impact on quality of life, mobility and independence[2,3]. All epidemiological studies conclude that, without prompt, concerted and well-designed prevention programs, the increasing costs related to these fractures will become an unbearable burden for the community within the next fifteen years[4]. However, the most effective way of setting up such preventive strategies is not yet unequivocally defined. Osteoporosis is a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk[5]. While this definition acknowledges the importance of age-related quantitative and qualitative skeletal defects, in the pathogenesis of osteoporotic fractures, it does not take into account other extraskeletal determinants that may significantly impact on the susceptibility to fracture, mainly at the hip level. Low muscle strength, poor balance and gait, all resulting in an increased propensity to fall also play a major role in the occurrence of hip fractures. In the present article, we will review the relative importance of the determinants of fracture in the elderly and we will try to identify those components that should be taken into account when defining what should ideally be an effective strategy for reducing spine and/or hip fracture incidence.

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Accepted 10 May 2003

Quantitative bone defect

A variety of techniques permit accurate and precise measurement of bone mass at different skeletal sites. *In vitro,* high correlation has been reported between bone mass and bone strength[6]. *In vivo*, bone mineral content (BMC) or bone mineral density (BMD) measured in an elderly subject is the result of two different phenomena, i.e., the level of peak bone mass achieved at the end of skeletal growth and the

rate of bone loss that occurs later in life, including the age-related bone loss found in both genders and the increased loss characteristic of the menopause in women. Low BMC/BMD has long been recognized as a major risk for fracture in the elderly. Retrospective[7], cross-sectional[8], or prospective[9] studies have all concluded that the risk of low-trauma fracture is negatively correlated with the amount of bone present in the skeleton. Measurements at the spine, hip or radius performed comparably in predicting the risk of any mild to moderate trauma fracture while, for the prediction of a site-specific fracture, measurement of BMC/BMD at the site in question dramatically improves the predictive value of bone densitometry. For example, a hip fracture is best predicted by hip bone density[9,10]. In prospective studies, age-adjusted relative risk of fracture at any site, per one standard deviation decrease in BMC/BMD at the spine, hip or radius was found to be, most of the time, between 1.5 and 2.0, while, for each one standard deviation decrease in BMC/BMD of the various regions of interest of the hip, the age-adjusted relative risk for a hip fracture was consistently above 2.5[11]. Based on this strong association between BMC/BMD and fracture risk, found to be as strong as the one between high serum cholesterol levels and the risk of cardiovascular diseases, the World Health Organization proposed an operational definition of osteoporosis using diagnostic categories based on BMC/BMD, i.e., an osteoporosis being diagnosed if the value for BMC or BMD is 2.5 or more standard deviations below the mean value of a young reference population (t-score $\geq$ -2.5)[12].

Several authors have also used the strong predictive value of BMD to develop models for estimating a subject's lifetime risk[13] or more recently 10-year risk[14] of having an osteoporotic fracture, based on bone density and age.

However, low bone density does not entirely account for an increased risk of fractures. Recent prospective, randomized, controlled trials assessing the anti-fracture efficacy of several new chemical entities used in osteoporosis have reported conflicting results about the relationship between an increase in BMD and a decrease in fracture rates. For alendronate, early changes in BMD appear to be a good predictor of response, in terms of future fracture reduction[15]. However, calcitonin[16] or raloxifene[17] were shown to decrease vertebral fractures by a rather similar magnitude to bisphosphonates, but with only marginal increases in spinal BMD. On the other hand, fluoride use, which has been repeatedly linked with dose-dependent increases in vertebral BMD, had not consistently reduced spinal fracture rates, particularly when given at high doses[18,19]. All these findings do not challenge the primary role played by low bone mass in skeletal fragility but they emphasize the fact that other independent determinants of fracture risk should not be minimized.

Decrease in bone quality

Factors other than bone quantity contribute to bone fragility. Subtle changes in bone quality may explain why the fragility of the skeleton in osteoporosis seems exaggerated in proportion to the reduction in bone mass. Predominant aspects of bone material properties include compositional and organizational variables[20]; the former category includes porosity and mineralization. Organizational features include trabecular and cortical bone architecture[21]. Porosity distinguishes between voids and solid matrix in bulk bone. Mineralization distinguishes between the mineral and organic components of the solid matrix and is the mass fraction of the mineral[20]. In principle, these two dimensions should be captured by BMC/BMD measurements.

The orientation and spacing of trabeculae influence the elastic modulus and failure stress of cancellous bone. The loss of connectivity is an irreversible process as new lamellar bone can only be added to existing surfaces. The mechanisms underlying the decrease in trabecular bone connectivity are still debated. Parfitt et al.[22] suggested that, following menopause, resorption cavity depth increases, allowing plates of normal thickness to be breached by osteoclasts working either from one side of the plate or from both sides simultaneously. Other explanations include a specific tropism of osteoclasts for thinner-than-average plates, a generalized thinning of plates occurring after the menopause, rendering them penetrable by resorption cavities of normal depth or a stochastic hypothesis stating that the probability of trabecular perforation is increased simply as a consequence of the increase in the activation frequency of remodeling units after menopause[23-25].

When evaluated by microcomputed tomography, the three-dimensional cancellous microstructure of bone samples from women with hip fractures shows lower bone volume fraction, lower trabecular number and lower connectivity than specimens from control subjects[26]. Biochemical markers of bone turnover have also been shown, in large prospective cohorts, to predict the risk of hip fractures to the same extent and independently of BMD. Their combination (low BMD and high bone resorption) significantly improves the predictive value, re-emphasizing that bone resorption influences bone biomechanical properties, through a distinct mechanism than simply increasing bone loss[27].

Trabecular bone that has no preferential axis of orientation (isotropic) will resist loads equally in any direction. In contrast, anisotropic specimens (contain axis of preferred orientation) will be stronger and stiffer when loading along the direction of dominant trabecular orientation and weaker when loaded along an axis where the trabeculae are less oriented[26]. Both trabecular and cortical bone are anisotropic[20]. While a simple Singh grading of hip radiographs can already discriminate between subjects having sustained a hip fracture and matched controls[28], fractal analysis of microradiography[29], micro-computed tomography[30] and high resolution magnetic resonance micro-imaging[31] are currently used to assess trabecular architecture *in vivo* and provide substantial addition to BMD for the understanding of the osteoporotic processes.

Anatomical determinants of biomechanical resistance

The strength of an object is a function of other properties, besides the mass and density of the material present. Strength depends on the mechanical properties of the material, on accurate knowledge of the object's geometry and the loading conditions, in terms of magnitude, rate and direction of forces applied to the object[32]. The gross anatomy (i.e., the shape and size) of a bone is in large part determined during growth. Modeling serves to sculpt the bone to suit both the genetic plan and the demands of current mechanical usage. In adults, modeling is reduced in rate and extent, so that alteration of bone geometry requires much more time[20]. When considering hip fracture, it seems thus reasonable to consider that the geometry should be related to hip strength, independently of femoral BMD.

Femoral geometry parameters include hip axis length, neck-shaft angle and femoral neck width, that all have been related to the mechanical strength of the proximal femur. In a cross-sectional study, comparing patients from both genders with hip fractures, whose measurements were taken in the contralateral hip, with matched controls, femoral neck BMD, neck-shaft angle and mean femoral neck width were significant independent predictors of hip fractures in both sexes[33]. Each increase in one standard deviation in neck-shaft angle or femoral neck width was associated with a two- to three-fold increase in the odds ratios of hip fracture. Such a relationship with hip fracture was also recently reported for the hip axis length, i.e., each standard deviation increase in hip axis length nearly doubled the risk of hip fracture, even after adjustment for femoral neck BMD[34,35]. However, measurement of the femoral neck axis length (similar measure of femoral geometry but does not include acetabular structure) failed to be useful in predicting hip fracture risk[36].

All these studies show that simple anthropometry proves to be a valuable enhancement of densitometry for the assessment of hip fracture risk and could justify a proactive approach to identify women in the community to whom a prevention strategy should be targeted[35].

Extraskeletal factors

Hip fractures are the most devastating and costly fractures in elderly women[1]. Surprisingly, very few medications that were shown to significantly reduce vertebral or forearm fracture rates, were also reported to be active against hip fractures. Recently, risedronate, a third-generation bisphosphonate reduced hip fracture incidence in women aged 70-79 years with severe osteoporosis (low BMD and prevalent vertebral fractures) but failed to do so in elderly women (>80 years) despite a significant effect on femoral BMD[37], hence stressing the importance of extraskeletal factors in the occurrence of hip fracture in the elderly. About 90% of hip fractures involve falls[38] and falling tendency has been identified as a predominant predictor of fragility fractures in women over 70 years[39]. The loads required to fracture the isolated elderly cadaveric femur, established during *in vitro* testing, are significantly smaller than the estimate of the potential energy generated during a typical fall from standing height[40]. The age-related decline in muscle function leads to an increased incidence of falls during standing and transferring and while the majority of falls in old age probably result from a combination of factors, gait disorders, loss of balance and decrease in muscular strength or function, all changes affecting postural control were systematically associated with falls[41,42]. Furthermore, the increase in hip fractures with age is not fully accounted for by the sole increase in the number of falls with age[38]. The characteristics of the fall are another key factor contributing to hip fracture risk[43]. Among women who fell on the hip, those with hip fractures were less likely to have landed on a hand or to break the fall by grabbing or hitting an object and were more likely to land on a hard surface than those without fractures[38]. Actually, the onset of a fall initiates several types of protective responses that may attenuate the force of impact and decrease the risk of a fracture. The effectiveness of protective responses in reducing the residual energy transmitted to the proximal femur is mainly determined by muscle strength and is therefore affected by the age-deterioration in muscle function as well[40]. Exercise programs based on increasing muscle strength, improving balance, gait, mobility and endurance resulted systematically in a drastic decrease in the number of falls[44-46], showing that effective measures to prevent falls in the elderly currently exist. Public health strategies should consider both: medications able to restore muscle strength and function, as well as these multi-intervention programs as a first priority to protect elderly individuals and reduce the economic burden raised from fall-related injuries.

Conclusion

Osteoporosis-related fractures result from a combination of skeletal and extraskeletal determinants. Depending upon the localization of the fractures, the relative importance of each of these risk factors can significantly differ. For prevention of vertebral fracture, drugs affecting bone mass and skeletal architecture may provide a substantial benefit, while hip fracture prevention will be more successfully targeted by multi-intervention strategies, taking into account not only the skeletal dimension of the fracture but also aiming, either pharmacologically or through multidisciplinary programs, at reducing the incidence but also the consequences of falls in the elderly.

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