Basis of Bone Strength vs. Bone Fragility: A Review of Determinants of Age-Related Hip Fracture Risk

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INTRODUCTION

The number of persons with hip fracture has increased during last decades worldwide. It was estimated that in 1990 about 1.66 million people sustained hip fracture [1]. Some data suggest further increase in hip fracture incidence, possibly reaching even more than 6 million affected people in 2050, which could be related to the increasing number of elderly people worldwide [1, 2].

Hip fracture incidence differs among the countries and races [3, 4]. The lowest incidence of 5.6 per 100,000 inhabitants has been recorded in South African Bantu [5], while hip fractures are most common on the North, particularly in Scandinavia. Namely, the incidence of hip fractures in Norway in people over 50 is 701 per 100,000 in females and 310 per 100,000 in males [6]. Analysis of patients over the age of 50 who sustained hip fracture in 1990-2000 period in Belgrade revealed the incidence rate of 143.6 per 100,000 persons [7]. Between 50% and 90% of all fractures occur in persons older than 70 years [8]. The consequences of hip fractures are severe for an individual, and quite expensive for the society. Namely, about 20% of patients die of hip fracture within the first 6 months, while a third of patients permanently loses ability to live independently without help of family or specialized geriatric service [2]. From economic perspective, treatment of patients with hip fracture represents a significant problem for health system, with direct annual costs of medical treatment estimated to be nearly 10 billion dollars in the USA [2].

Extensive research was undertaken during the past decades in order to improve the knowledge about age-related hip fractures. The initial epidemiological studies were directed towards identifying risk factors [3, 4]. Subsequently researchers tried to find the way for early detection of persons at a risk, which led to a particular focus on bone mineral density (BMD), where a BMD was suggested to be a predictor of hip fracture risk. However, given that a low BMD cannot fully explain the development of fractures, more recent studies have focused on various structural or compositional bone features that account for bone quality.

Apart from falls [9], the risk of hip fractures in the elderly is associated with numerous bone features that degrade bone strength. It is well established that bone strength depends both on “bone quantity” and “bone quality” [10]. Assessing the “bone quantity” requires measuring BMD and geometric characteristics of the bone, while the “bone quality” involves bone microarchitecture, microdamage accumulation, degree of remodeling, mineralization level and collagen cross-links [10].

In this review, we shall focus on the complexity of bone features that could account for increased bone fragility in advanced age.

BONE MINERAL DENSITY

BMD (g/cm²), measured by dual energy X-ray absorptiometry (DXA), is widely accepted as a measure of bone mass and predictor of hip fracture susceptibility. BMD of a particular region depends on bone mineral content (BMC; g) per given area. Maximum values of density are reached in late adolescence, after which it remains stable for a certain period, and then bone mass starts to decline. The age-related decline is gradual in men, while in women there...
is acceleration in the loss of bone mass after menopause. However, the diameter of long bones continues to increase during aging due to the persistence of periosteal apposition process [11]. Pronounced endosteal resorption leads to cortical thinning and decline in bone mineral mass which is reflected in lower BMD. Another significant reason for additional decrease in BMD is increased total area due to periosteal apposition [11, 12]. The decrease in BMD explains a significant part of fracture risk [13] and is statistically related to bone strength [14]. Each standard deviation of decline in BMD increases the fracture risk by 50-150% [15]. World Health Organization (WHO) recommends measuring BMD as the “gold standard” for fracture risk assessment [16]. T-score is the number of standard deviations below or above the average BMD of young healthy adults of the same sex, while Z-score depicts the number of standard deviations above or below the average BMD of age- and sex-matched controls [16]. According to the WHO criteria, more than 2.5 standard deviations decrease in BMD defines osteoporosis [16].

However, more recent studies have shown that BMD cannot be a reliable predictor of fracture risk, since there is a partial overlap in BMD values in patients with hip fractures and healthy persons [17]. Moreover, only 28% of fractures in women aged 65-84 years can be explained by low BMD [18], and De Laet et al. [19] reported 13-fold increase in fracture risk accompanied by only 2-fold decrease in BMD between 60 and 80 years of age.

**BONE EXTERNAL GEOMETRY**

The initial studies that assessed external geometry of the hip have found statistically significant relationship between longer femoral neck and increased hip fracture risk [20]. The studies on bone geometry helped to explain a part of differences in fracture incidence between the races; for instance, the Japanese have a lower hip fracture incidence than the Americans despite the lower BMD since they have also a shorter femoral neck [21]. Geometric parameters of the femur in radiographs were analyzed in persons with and without hip fracture revealing a larger collo-diaphyseal angle in patients with fracture, in contrast to a smaller intertrochanteric width, and thinner femoral neck and shaft cortices [22]. However, although measures of bone external geometry are useful, they still do not take into account the bone internal structure, and therefore explain the bone strength only partly.

New approach in analysis of femoral geometry was established by Beck et al. [23]. They have designed HSA software (hip structure analysis) that uses DXA image to extract estimates of some specific mechanical properties of the bone section (moment of inertia, section modulus, buckling ratio), together with some of bone internal architectural features (cortical thickness, centroid position). HSA-derived mechanical parameters reflect the degree of proximal femoral resistance to compression and bending. Application of HSA method on cadaveric samples from the Balkans have revealed that age-related changes in men are most intensive in the femoral neck region, while in women the changes are also pronounced at intertrochanteric region [12]. Therefore, the neck region in men represents the critical site for age-related low-trauma fracture, while in women intertrochanteric region presents as an additional weak spot [12]. These results are in concordance with epidemiological data that older men have more cervical than trochanteric fractures, while in women apart from cervical, trochanteric fractures also increase significantly with aging [24].

**TRABECULAR AND CORTICAL MICROARCHITECTURE**

Besides external geometry of bone, remarkable bone internal structure has been the subject of more recent studies. There is a growing interest in bone microarchitecture as a determinant of bone strength. However, the relative contribution of trabecular vs. cortical microarchitecture to bone strength is still obscure [25].

A number of studies have reported that trabecular bone loss that happens with aging reduces bone strength and increases fracture susceptibility [26]. It was reported that even 80% of variations in trabecular bone mechanical properties could be explained by its architecture [27]. Furthermore, significant differences in trabecular microarchitecture were found in the femoral head [28] and femoral neck [29] of women with hip fracture vs. controls, supporting significance of the trabecular bone features for bone fragility. Moreover, the observed architectural differences in the femoral neck are region-dependent, i.e., they are more pronounced at its lateral portion than in the medial [29], which is compatible with the lateral neck being an initiating site of fracture.

Nazarian et al. [30] underlined regional variations in densitometric, morphometric and mechanical properties within the femur. A number of studies have contributed to the view that aging does not lead to uniform changes in all proximal femoral subregions. There is a fixed stream of studies showing that the lateral subregion of the femoral neck undergoes bone loss before and more extensively than the medial neck in women [31], men [32] and both sexes [33, 34]. Although Lundeen et al. [31] have hypothesized that it is not the characteristic of entire population but only some individuals with unknown predisposing factors, some recent studies suggest otherwise [32, 34]. In a recent micro-CT study on trabecular microstructure of three biomechanically relevant subregions of the proximal femur (medial neck, lateral neck and intertrochanteric region), Djuric et al. [34] demonstrated clear microarchitectural differences between those sites in both sexes and that the aging process is not uniform in an individual. Namely, apart from initial inter-site differences, trabecular microarchitecture changes differently with aging depending on the subregion [34]. Aging was found to affect most the intertrochanteric region in women and the lateral neck in men, while the medial neck was relatively “immune” to aging in both sexes [34].

Age-related cortical thinning also is not uniform within the femoral neck; namely, the cortex is particularly thinned
in the underloaded region of the lateral neck which becomes severely loaded during a fall [12, 35]. Cortical thinning was reported to be a dominant feature in femoral neck fracture [35]. Apart from decreased cortical thickness, an age-related increase in cortical porosity has been linked to decreased tensile strength of the bone [36], and individuals with hip fracture displayed not only thinner but also more porotic cortex [35, 37]. However, apart from higher number of pores, increased porosity in the femoral shaft cortex in the elderly could be a consequence of greater pores size [38]. Some authors found no age-related changes in number or size of pores, but changes in pores distribution, where porosity was unevenly distributed along the cortex, being particularly pronounced at the endosteal cortex of women leading to cortical thinning [39].

MICRODAMAGE AND BONE REMODELING

Microdamage and excessive remodeling may also play a role in fracture susceptibility [40]. Normal physiological loading during life causes local microfractures. However, bone has a remarkable ability to detect and repair the damaged regions using remodeling process. Development of microdamage is generally beneficial, since it is the way of dissipating the energy of load and preserving bone integrity. However, excessive accumulation of microfractures hampers bone mechanical properties and makes it prone to a macrofracture. Accumulation of microcracks in bone tissue during life-time [41] is the consequence of delayed or unsuccessful remodeling process [42, 43]. Osteocytes, the most numerous bone cells, are nowadays considered as key players in detecting microdamage and launching the remodeling process. Therefore, age-related decrease in osteocyte lacunae per bone area which is found in older individuals [42] might impede bone repair mechanism, particularly in terms of hampered detection of microcracks. Given that osteocytes are key mechanosensory cells of bone [43], changes in their number and sensitivity may have a significant influence on bone mechanical competence. Apart from age-related decline in osteocyte numbers, the elderly individuals have a considerable number of hypermineralized osteocyte lacunae which increase bone matrix brittleness and subsequently increase the fragility of the bone as a whole [42].

BONE AS MATERIAL

Generally, bone strength as a whole depends not only on macroscopic and microscopic parameters of bone structure, but also on the characteristics of the very material of which bones are composed. As a material, bones are a natural nanocomposite made of two major components: mineral matter (hydroxyapatite) and organic phase (collagen and the so-called non-collagenous proteins) [44]. As a nanocomposite material, bone has better mechanical properties than each of the components individually [45].

Despite agreement that bone mineral extensively influences bone mechanical properties, the totality of its effects is largely unknown [46]. Apart from amount of bone mineral, it is suggested that the properties of mineral (such as its chemical composition, crystallinity, shape and size of crystals) also determine bone strength [47, 48, 49]. The higher the degree of bone matrix mineralization, the lesser the degree of plastic deformation before fracture that can be withheld by bone [46]. It is known from the science of materials that crystal size affects material mechanical properties in the sense that small-grained materials are mechanically stronger than the large-grained ones [50].

From that aspect, a part of the basis of bone fragility in elderly women has been clarified by a recent atomic force microscopy (AFM) study which showed a larger average mineral grain size in trabecular bone samples from the femoral neck of elderly women in comparison to younger women [48]. Based on the unchanged amount of mineral and larger mineral grain size in the elderly, it seems that the existing mineral grains possibly reorganize during aging by aggregation [48]. Such nanostructural features of aged bone material are accompanied by a decreased elasticity, as shown in a recent AFM nanoindentation study [49].

It is certainly not only the mineral which is modified during aging that the organic part of the bone matrix is also subject to changes. Recent studies examined collagen and pointed out some differences in its structure and elasticity in senescence [51] and changes in collagen cross-links in osteoporotic patients [52]. However, the significance of collagen and non-collagenous proteins and their age-related changes are yet to be studied.

CONCLUSION

Although BMD is a current clinical indicator of the degree of the risk of age-related fractures, this parameter is only partly responsible for bone mechanical strength and decline in BMD cannot explain all fracture cases in the elderly. In order to have a more thorough assessment of fracture risk, it is essential to provide integrative approaches that combine BMD measure with other relevant bone features. For instance, some recent studies suggested combining BMD with DXA-based trabecular bone score (TBS) that crudely reflects trabecular architecture [53], combining BMD with geometric indices extracting mechanical data from DXA images [11-12], or direct measuring of bone mechanical properties by microindentation in vivo [54], and the use of non-invasive Raman spectroscopy to estimate bone composition [55]. In addition, understanding of various bone features associated with increased bone fragility might also provide new strategies for the problem of periprosthetic bone loss that is responsible for implant failure in operated hip fracture cases [56].

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REFERENCES


