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REVIEW

Structural basis of increased bone fragility in aged individuals: multi-scale perspective

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Summary

Numerous epidemiological studies have shown that increased bone fragility and a higher risk of fractures are present in the aged, which reduces their quality of life and represents a significant socio-economic burden for the healthcare system. However, morphological and structural determinants underlying increased bone fragility have yet to be fully explained. This paper aimed to provide an overview of modern studies that dealt with determinants of increased bone fragility, analyzing different hierarchical levels of bone tissue organization (macro-, micro-, and nano-levels) in aged individuals and individuals with chronic comorbidities (mainly in individuals with chronic liver disease, renal disorders, and type 2 diabetes mellitus). Also, variable frequency of fractures at different skeletal sites in aged persons and individuals with chronic diseases was shown, indicating that aging-related bone loss is not a uniform process. A complete understanding of the spatial pattern of impaired bone quality can aid in the targeted evaluation of individualized fracture risk. Establishing a firm connection between the results of the clinical assessment of bone status and the analysis of numerous structural and mechanical bone properties (on various hierarchical levels) can represent a solid base for developing adequate guidelines and algorithms for prevention and treatment of increased bone fragility in aged individuals and individuals with chronic diseases.

Keywords: bone fragility, ageing, bone fracture, hierarchical bone organization, bone strength

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INTRODUCTION

Bone fractures are a significant public health concern that affects a considerable proportion of the global population, mainly aged individuals, but also individuals with various chronic comorbidities (1,2). Aging-related bone fragility can result in serious health consequences, leading to disability, reduced quality of life, and increased mortality (3,4). In addition, aging-related bone fragility has significant socioeconomic consequences (5). As a population ages, the number of individuals at risk for fractures increases, which puts greater demands on healthcare resources due to an increased need for hospital admissions, rehabilitation, and long-term care (6–8). Given that bone fractures are preventable, it is essential to fully understand how they occur, and which factors contribute to increased bone fragility in aged individuals and individuals with chronic comorbidities. By addressing the issue of aging-related bone fragility, we can improve individuals' health and well-being, reduce healthcare costs, and promote healthy aging.

Bone fractures in aged individuals most frequently appear at the femoral neck, radius, and vertebral column, with a predilection to affect postmenopausal women (9–11). Moreover, bone fractures in these individuals commonly occur due to low-energy trauma (predominantly due to a fall from a standing height) (12,13). If we want to fully understand the reasons for increased bone fragility in aged individuals (especially those aged 65 years and over) (14) and individuals with chronic diseases, we should consider two main factors: 1) the mechanical loads applied and 2) bone strength (resistance to fracture) (15,16). It is known that a mechanical impact generated during low-energy trauma *per se* could not be sufficient to cause bone fracture (17). Hence, the leading cause behind increased bone fragility in aged individuals must originate from characteristics of the bone itself. So, we must reject the common perception of bone as a simple unviable mineral connective tissue that provides structural support, protects internal organs, and facilitates movement, and put our best efforts into understanding bone as metabolically active and dynamic tissue.

STRUCTURAL MORPHOLOGY OF BONE TISSUE: SHORT OVERVIEW

Since bone tissue is a living and dynamic system made of complex nanocomposite material, it has different structural organization and morphology at different length scales **(Figure 1)**, allowing it to withstand mechanical

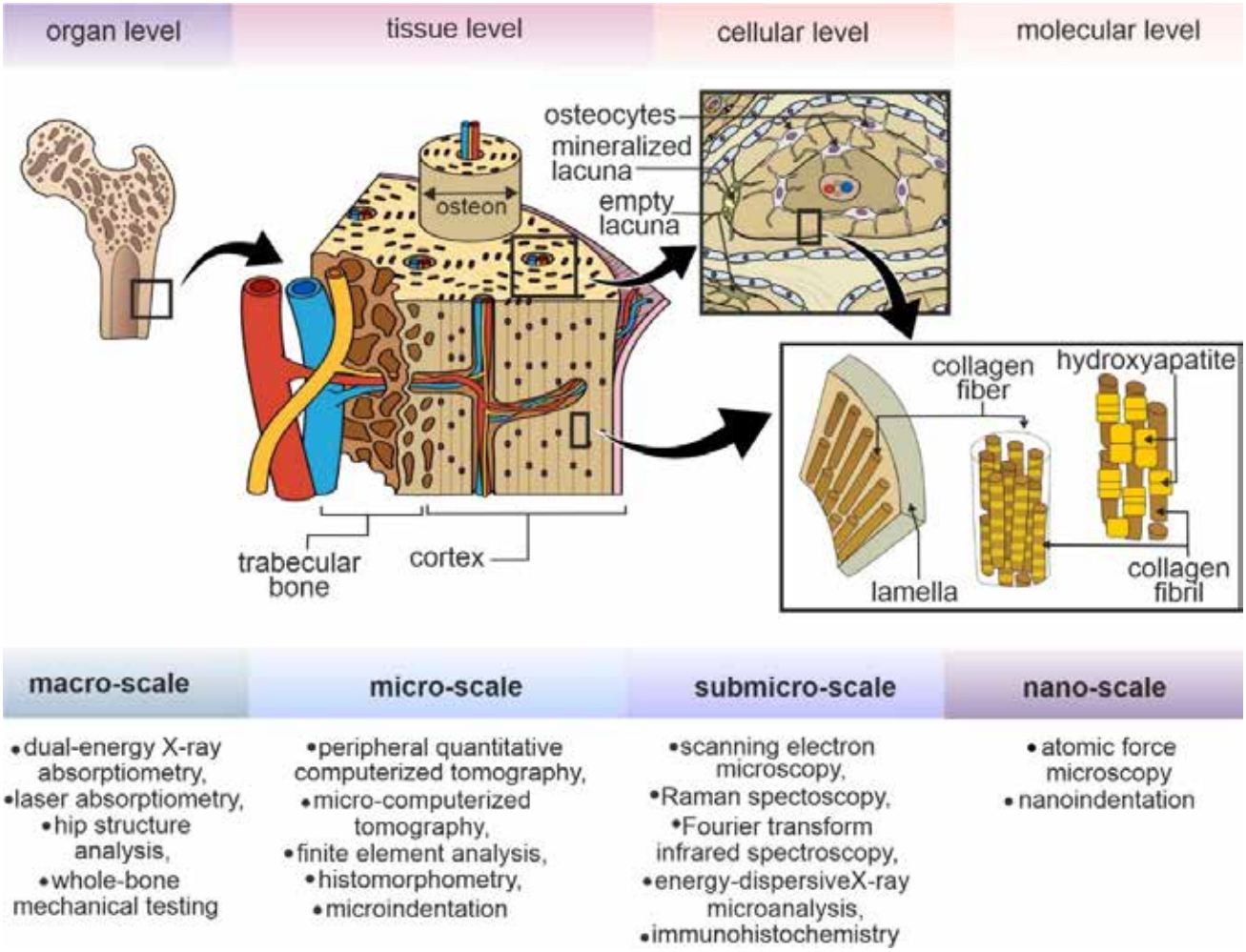

Figure 1. A schematic representation of the bone tissue hierarchical organization and methodology used for multi-scale bone assessment

loads while maintaining its structural integrity (18,19). Firstly, macroscopic observation shows the bone shape, size, and geometry (Figure 1), while cross-sectional analysis allows a distinction between two bone compartments: cortex (outer layer of bone tissue with a low porosity) and cancellous bone (porous bone tissue consisting of a network of interconnected bone trabeculae) (20). Microscopic evaluation of bone tissue reveals basic morpho-structural units predominantly found in cortical bone, known as osteons (21,22). Most of the bone volume is occupied by the bone matrix, inhabited by cells with specific functions: bone-forming cells called osteoblasts, bone-resorbing cells called osteoclasts, and the most numerous cells that act as bone remodeling orchestrators known as osteocytes (18,23). Going further to the submicroscopic level, it is evident that osteons consist of several concentric rings known as lamellae, while one lamella is made of many collagen fibers (Figure 1). At the nano-level, it is evident that each collagen fiber comprises many collagen fibrils immersed in an inorganic mineral component – hydroxyapatite crystals (19,24). Mineralized crystals and collagen fibers are combined in a highly organized manner to ensure that resistance to mechanical load is beyond the sum of mechanical characteristics of individual bone constituents (25,26).

Since bone is subject to morphological changes during aging (27,28) and various chronic diseases (such as chronic liver diseases, renal disorders and type 2 diabetes mellitus) (29–31), it is essential to investigate which bone characteristics (and at what hierarchical level of organization) could contribute to aging-related and disease-related bone fragility. Even though modern science is witnessing a significant breakthrough in technical inventions of bone-assessing medical imaging **(Figure 1)** (32), entirely accurate, reliable, and clinically relevant methods to assess bone fragility in aged individuals and individuals with chronic comorbidities are yet to be invented.

CLINICAL ASSESSMENT OF FRACTURE RISK: ADVANTAGES AND LIMITATIONS

Although recent attempts have been made to create a roadmap for improving global musculoskeletal health (33), there are still many unresolved issues in clinical assessments of fracture risk. Namely, the "golden standard" in the clinical estimation of the fracture risk is areal bone mineral density (aBMD) obtained by dual-energy X-ray absorptiometry (DXA). It is defined as bone mineral content (BMC; g) per analyzed bone area. The peak of aBMD values is reached in late adolescence, after which it remains stable, and then bone mass starts to decline (7,18,34). Aging-related bone loss is gradual in men, while accelerated bone loss is pronounced in postmenopausal women (13,35) due to the negative net bone balance (a decline in bone formation could not compensate for bone resorption) driven by hormonal dysregulation (34). Also, increasing the outer diameter and thinning of the cortical bone (periosteal apposition and endosteal resorption occur in a sex-specific manner during aging), contributing to increased bone fragility in aged individuals (36–38).

It is clear that a single two-dimensional parameter, such as aBMD, cannot fully reflect the fracture risk since many studies have suggested that eliminating low aBMD in aged individuals would reduce the risk of fractures only modestly (13,39). Moreover, the bone mass of individuals who sustained a bone fracture and those who did not experience bone fracture overlap considerably, indicating that bone mass and aBMD are insufficient for individual fracture risk prediction. Also, it has been known that some pharmaceutical agents used to treat osteoporosis positively affect bone strength and decrease fracture risk without increasing aBMD (40,41), indicating the necessity of using other bone characteristics in individualized fracture risk assessment.

Several attempts have been made to overcome the limitations of using aBMD for fracture risk assessment. Among them, DXA-based hip structure analysis (HSA) of the proximal femora allowed for estimating specific biomechanical indices of femoral bone strength (42,43). Indeed, despite its limitations, the HSA showed better sensitivity to predict hip fracture than areal BMD measurements alone (44) and improved understanding of the changes in bone strength components in aging and chronic diseases (45,46). Realizing that bone internal architecture is essential for fracture risk assessment, another valuable clinical tool, known as trabecular bone score (TBS), was developed (47,48). This grey-level textural measurement indirectly estimates bone microarchitecture from DXA images of lumbar vertebral column. Recent clinical studies have confirmed the fracture-discriminating ability of TBS in a substantial number of postmenopausal women (47,48). However, a significant limitation of this methodology is that it could be applied to one skeletal site only (L1-L4 vertebrae)(49). Also, another clinical fracture risk assessment tool, known as Fracture Assessment Tool (FRAX) was developed to demonstrate the 10-year probability of a hip fracture and of a major osteoporotic fractures (50,51), but it fails to recognize the impact of other non-skeletal fracture risk determinants (balance disturbances, reduced vision, and altered motor coordination that can cause an increased risk of falling) (50,51).

In clinical settings, histomorphometric analysis of transiliac bone biopsy samples has been used to quantitatively evaluate the bone status and effects of certain anti-osteoporotic therapies of bone tissue collected from aged patients (52–54) and patients with chronic comorbidities (55,56). Besides histomorphometry being an invasive procedure that allows 2D micro-scale bone assessment **(Figure 1)**, concerns remain because the iliac crest is not representative of various skeletal sites, given that osteoporosis is not a uniform process throughout the

skeleton. In addition, a modern noninvasive 3D *in vivo* method for clinical bone assessment at the distal radius and tibia is high-resolution peripheral quantitative computed tomography (HR-pQCT) (57–59). The radius and the tibia undergo different mechanical loading patterns (60) and have different fracture risks concerning age and sex, however these fractures are not the most frequent and not the most severe ones either. Nevertheless, numerous studies used HR-pQCT to address cortical and trabecular properties of the tibia and the radius in aged individuals (9,18). Also, an increasing number of studies is using HR-pQCT to reveal altered cortical and trabecular micro-architectural properties in individuals with diabetes mellitus (61), chronic kidney disorders (62) and liver diseases (63). Even though HR-pQCT analyses could provide better predictive accuracy of fracture risk assessment beyond aBMD measurements, it is yet to develop full potential due to high associated cost, limited voxel size (82 μm), and inability to access the most relevant fracture sites (proximal femora and vertebral column) (18). Considering the shortcomings of current methodology, it is of great importance to develop a better diagnostic algorithm that would allow reliable clinical fracture risk assessment in aged population and individuals with various chronic comorbidities.

MULTI-SCALE BONE ANALYSIS: REVIEW OF CURRENT LITERATURE AND FUTURE RESEARCH DIRECTIONS

Various factors (skeletal and non-skeletal) contribute to changes in fracture risk in aged individuals and individuals with chronic comorbidities that cannot be detected through bone mineral density. Commonly described as non-skeletal factors associated with higher fracture risk in aged individuals are sarcopenia, higher risk of falls, poor vision, altered motor coordination, therapeutic side effects, and disease complications (50). Among skeletal factors, the most significant attention in modern research is paid to impaired "bone quality"— generally referring to intrinsic bone properties (beyond aBMD) that influence mechanical performance (15,16).

In previous years, the relative contribution of micro-scale bone quality features to bone strength has been examined extensively. Namely, the aging-related trabecular micro-architectural decline is presented as a loss of trabecular elements, declined trabecular connectivity coupled with trabecular thinning observed at the proximal femora, vertebral bodies, the radius and tibia of aged individuals (64–66). Along with trabecular micro-architectural bone loss **(Figure 2)**, increased cortical porosity

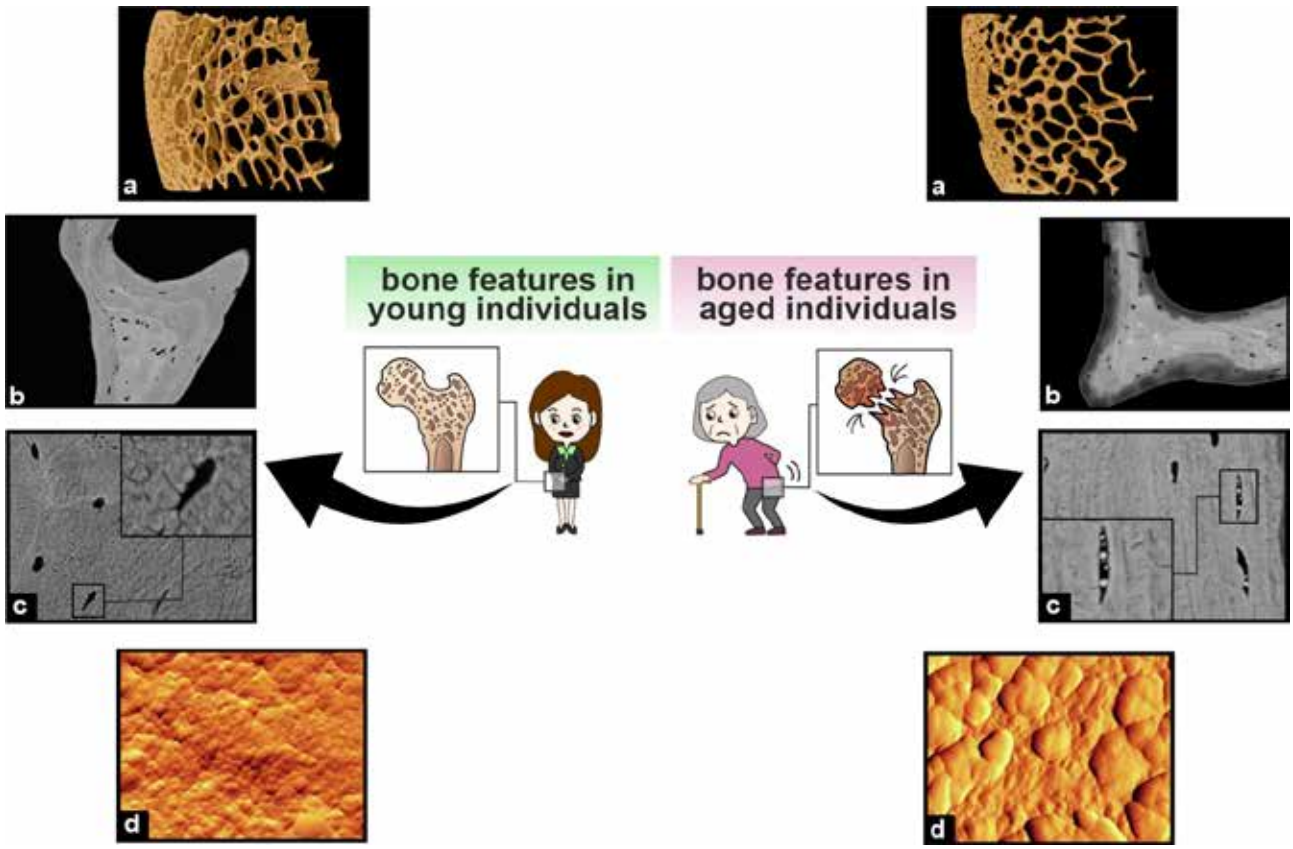

Figure 2. Small-length bone fragility determinants associated with ageing: graphic summary. Note significantly deteriorated bone micro-architecture (a) and altered bone tissue mineral content in aged individual (b). Moreover, osteocyte lacuno-canalicular network disruptions, increased number of mineralized osteocyte lacunas - micropetrosis (c), coupled with larger mineral crystal size (d) were demonstrated to contribute to aging-related bone strength reduction. However, the particular effects of various chronic diseases on these bone quality features are yet to be fully elucidated.

(originating from accumulation of incompletely closed osteons and resorption cavities) and cortical thinning are proven to contribute to bone fragility in aged individuals (11,64) and individuals with chronic liver diseases (29) and renal disorders (55). Moreover, it is becoming clear that spatial distribution of skeletal alterations and decline in intrinsic bone properties contribute to increased susceptibility to bone fracture in a site-specific manner (7,67). Namely, our team noted significantly different micro-architectural properties in the proximal femora, with different aging patterns between genders: the most prominent effect of aging in males was noted in the superolateral femoral neck (common fracture-initiating site), while the intertrochanteric region was most severely affected in females (65). These results support epidemiological data about the various occurrence of cervical and intertrochanteric fractures in older men and women (65). Also, having observed various levels of micro-architectural decline in the proximal femora, our team noted that the effect of chronic alcoholic liver diseases was not uniform, supporting epidemiological data about the association between chronic liver disease and heavy alcohol consumption and increased incidence of unstable intertrochanteric femoral fracture (46). Also, it was reported that duration, stage and severity of the disease could be an important risk factor for advanced bone alterations in individuals with chronic liver diseases (63,68). Lastly, it was revealed that vascular complications were important risk factor for femoral bone microstructural decline in individuals with type 2 diabetes mellitus (69), while hemodialysis was reported as a major risk factor for bone loss in patients with chronic kidney disease (70).

Conversely, the role of submicro- and nano-scale features is more difficult to study, especially *in vivo* or in clinical settings, pointing out that many questions related to these bone properties need to be explored to complete the bone fragility puzzle in aged individuals and individuals with chronic comorbidities. Recent studies revealed a shift to higher bone mineralization, reduced osteocyte lacunar density, and increased number of mineralized osteocyte lacunae (micropetrosis), coupled with deterioration in the lacuno-canalicular network which reduces the connectivity between osteocytes in the aged individuals (71–74). Moreover, a few state-of-the-art studies reported that increased mineral crystal size **(Figure 2)** could contribute to a decline in aging-related bone strength (24,27). On the other hand, micropetrosis was only recently investigated in individuals with chronic kidney disease (75), and its role in bone fragility of individuals with chronic liver diseases and type 2 diabetes is yet to be explored. Moreover, further research is needed to fully understand the contribution of each bone fragility determinant on various hierarchical levels of bone tissue (especially in relation to specific chronic disease), given that these data are a valuable resource that could (in integration with clinical data) make a solid base for generating specific algorithms for timely preventive and therapeutic measures for bone fragility related to aging and various chronic diseases.

CONCLUSION

Increased bone fragility is a common health problem in aged population and individuals with chronic diseases (especially chronic liver and kidney disease, and type 2 diabetes mellitus). Numerous studies have contributed to understanding the morpho-structural base of skeletal damage caused by aging and disease, but innumerable ambiguities remain. Thus, further research is necessary to solve the bone fragility puzzle in these individuals. Considering the need for patient-specific clinical guidelines for the prevention and treatment of compromised bone strength and its complications, the long-term benefit of multi-scale and advanced assessment of bone fragility could be in developing a specific diagnostic algorithm that will help to reliably predict bone strength based on the information available in the clinical context of each patient.

Author contribution statement

Conceptualization: all authors; Data acquisition: Jelena Jadzic; Data interpretation: both authors; Data visualization: Jelena Jadzic; Writing – original draft: Jelena Jadzic; Writing – Review and Editing: Marija Djuric; Project administration and Funding acquisition: Marija Djuric; Approval of the submitted manuscript version: both authors.

Ethical approval and patient consent

Not applicable.

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STRUKTURNE DETERMINANTE POVEĆANE KOŠTANE FRAGILNOSTI KOD STARIJIH OSOBA: VIŠESTRUKE PERSPEKTIVE

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Sažetak

Mnogobrojne epidemiološke studije su pokazale da je povećana fragilnost kosti i veći rizik od preloma prisutan kod starijih osoba, što redukuje kvalitet života i predstavlja značajan socio-ekonomski teret za zdravstveni sistem. Ipak, mofrološke i strukturne determinante koje leže u osnovi povećane koštane fragilnosti ovih osoba nisu u potpunosti razjašnjene. U ovom radu dat je pregled rezultata savremenih studija koje su se bavile determinantama povećane koštane fragilnosti analizirajući različite hijerarhijske nivoe organizacije koštanog tkiva (makro-, mikro- i nano-nivo) kod starijih osoba i osoba sa hroničnim oboljenjima (prevashodno sa hroničnim oboljenjima jetre, hroničnim bolestima bubrega i šećernom bolesti tipa 2). Takođe, pokazana je varijabilna učestalost preloma na različitim skeletnim mestima starijih osoba i osoba sa hroničnim oboljenjima, što ukazuje na to da gubitak kvaliteta kosti nije uniforman proces. Potpuno razumevanje prostornog obrasca narušenosti kvaliteta koštanog tkiva može pomoći u ciljanoj evaluaciji rizika od preloma kod svakog pojedinačnog pacijenta. Uspostavljanje veze između rezultata kliničke procene koštanog statusa i analize brojnih strukturnih i mehaničkih svojstava kosti (na različitim hijerarhijskim nivoima) može da predstvalja osnovu za razvoj adekvatnih vodiča i algoritama za prevenciju, dijagnozu i lečenje povećane koštane fragilnosti kod starijih i osoba sa hroničnim oboljenjima.

Ključne reči: fragilnost kosti, starenje, prelom kosti, hijerarhijska organizacija koštanog tkiva, čvrstina kosti

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