

Review

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Tim Rolvien and Michael Amling*

Bone biology in the elderly: clinical importance for fracture treatment

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Abstract: Age-related bone impairment often leads to fragility fractures in the elderly. Although excellent surgical care is widely provided, diagnosis and treatment of the underlying bone disorder are often not kept in mind. The interplay of the three major bone cells – osteoblasts, osteoclasts, and osteocytes – is normally well regulated via the secretion of messengers to control bone remodeling. Possible imbalances that might occur in the elderly are partly due to age, genetic risk factors, and adverse lifestyle factors but importantly also due to imbalances in calcium homeostasis (mostly due to vitamin D deficiency or hypochlorhydria), which have to be eliminated. Therefore, the cooperation between the trauma surgeon and the osteologist is of major importance to diagnose and treat the respective patients at risk. We propose that any patient suffering from fragility fractures is rigorously screened for osteoporosis and metabolic bone diseases. This includes bone density measurement by dual-energy X-ray absorptiometry, laboratory tests for calcium, phosphate, vitamin D, and bone turnover markers, as well as additional diagnostic modalities if needed. Thereby, most risk factors, including vitamin D deficiency, can be identified and treated while patients who meet the criteria for a specific therapy (i.e. antiresorptive and osteoanabolic) receive such. If local health systems succeed to manage this process of secondary fracture prevention, morbidity and mortality of fragility fractures will decline to a minimum level.

Keywords: bone remodeling; DXA; fragility fractures; HR-pQCT; osteoporosis; secondary fracture prevention; vitamin D.

Introduction

Osteoporosis is the most common skeletal disorder characterized by low bone mineral density (BMD), impaired bone quality, and fragility fractures [1]. It is furthermore regarded as a polygenic condition in which aging, lifestyle factors, and several unfavorable single nucleotide polymorphisms (SNPs) as well as other genetic variants lead to increased skeletal fragility [2]. Fragility fractures are very common and affect one in two older women and one in three older men [3]. Whereas vertebral fractures are the most frequent osteoporotic fractures, proximal femur fractures have the most severe outcome, causing 24.5%–36% mortality in the first year after fracture [4, 5]. In the aging population, fracture rates have reached epidemic levels in the Western Hemisphere. The subsequent loss of mobility and autonomy often constitute a drastic drop in the quality of life.

The diagnostic gold standard of fracture risk assessment is a BMD scan by dual-energy X-ray absorptiometry (DXA), measuring the proximal femur and the lumbar spine. The World Health Organization defines osteoporosis as BMD of lower than 2.5 standard deviations below average as assessed by DXA measurements (T-score; Figure 1A). However, fracture risk depends on many more factors such as age, gender, or hormonal status. Therefore, there is a relevant proportion of patients with a T-score higher than –2.5 suffering from fragility fractures. Although age is a risk factor for osteoporosis, it is often mistakenly assumed that osteoporosis might be a natural phenomenon if one lives long enough [6]. In Germany, 6.3 million patients suffer from osteoporosis, of which only one quarter receives specific treatment [7]. The surgical treatment of fractures is performed on a very high level nowadays, although the underlying causes for fractures remain underdiagnosed.

In addition to DXA, extended laboratory tests of calcium homeostasis and bone turnover are useful to exclude secondary causes for fragility fractures. Here, prominent examples are osteomalacia caused by vitamin D deficiency [low 25-OH-D₃, elevated alkaline phosphatase, elevated parathyroid hormone (PTH)], calcium malabsorption due to hypochlorhydria (low calcium, elevated gastrin), multiple myeloma (high calcium, high creatinine,

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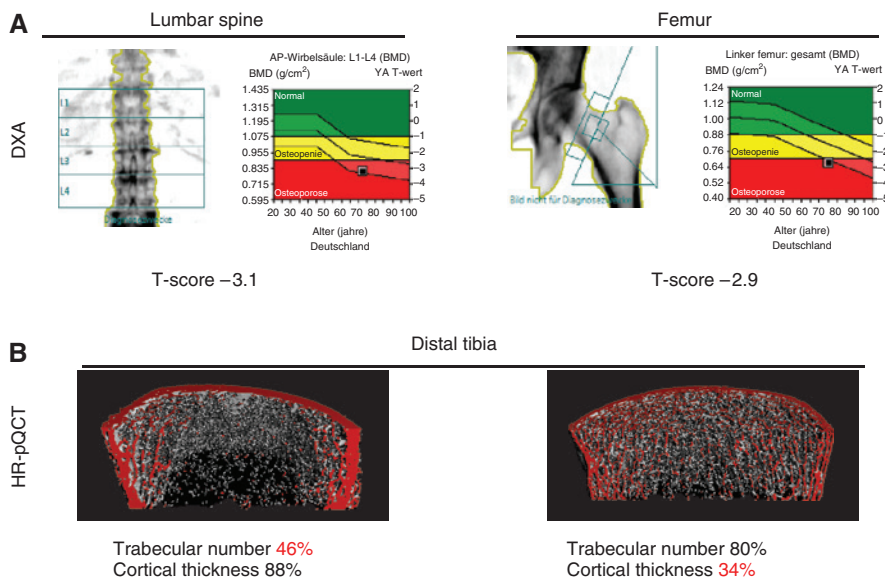


Figure 1: Diagnostic modalities of osteoporosis.

(A) DXA bone scans of the lumbar spine and proximal femur reveal a low BMD. A standard deviation of 2.5 below the average of a young adult (T-score < -2.5) is defined as osteoporosis. However, a statement on the volumetric parameters cannot be made. (B) HR-pQCT offers a possibility to assess the patient's bone structure in terms of cortical and/or trabecular bone loss, whereas both lead to increased risk of fracture (% compared to reference values).

γ -peak in protein electrophoresis), primary hyperparathyroidism (elevated calcium, elevated PTH), or renal osteodystrophy (decreased 1,25-OH₂-D₃, increased PTH). Table 1 lists the relevant serum markers in the differential diagnosis of osteoporosis.

Apart from DXA, another helpful tool for osteoporosis diagnostics is high-resolution peripheral quantitative computed tomography (HR-pQCT; Scanco Medical, Switzerland), which assesses the three-dimensional bone microstructure in the cortical and trabecular bony compartment as well as bone mineralization (Figure 1B). This way, trabecular and cortical bone loss syndromes can be uncovered, while both may lead to increased risk of fracture [8].

In patients with degenerative diseases such as osteoarthritis in the lumbar spine, where DXA BMD values are falsely high, HR-pQCT offers a valid diagnostic alternative.

In general, it is of high importance to perform osteologic diagnostics after any fragility fracture has occurred to provide the best long-term medical care. Also, the diagnostic procedures have to be carried out even before the first fracture, especially if any risk factors such as immobilization, diabetes, or corticosteroid therapy are present. Because fragility fractures affect most commonly elderly patients, the German guidelines recommend the basic osteoporosis diagnostics independently from risk factors for women ages 70 years above and men ages 80 years and

Table 1: Laboratory parameters to identify the causes for imbalances in calcium homeostasis and osteoporosis (only selected conditions).

Parameter	Low	High
Calcium	Vitamin D deficiency, hypochlorhydria, hypoparathyroidism, renal insufficiency (renal loss), secondary hyperparathyroidism	Primary hyperparathyroidism, tumor (i.e. multiple myeloma), sarcoidosis
Phosphate	Vitamin D deficiency, hyperparathyroidism, renal insufficiency (renal loss)	Elevated intake, rhabdomyolysis, renal insufficiency
Alkaline phosphatase	Hypophosphatasia	Liver disease, Paget's disease, osteomalacia
25-OH-D ₃	Insufficient intake or production in the skin	Vitamin D intoxication (very rare)
PTH	Hypoparathyroidism	Primary, secondary, or tertiary hyperparathyroidism
Osteocalcin/P1NP	Low turnover osteoporosis	Teriparatide
Deoxypyridinoline/ β -CTX (urine)		High turnover osteoporosis, vitamin D insufficiency, hyperparathyroidism, hyperthyroidism

P1NP, Procollagen type 1 amino-terminal propeptide; β -CTX, β -crosslaps.

above. In the following sections, we outline the basics of bone biology, which are fundamental to understand the differential diagnostics and therapeutic options of osteoporotic fractures. The optimization of fracture healing and long-term therapy of osteoporosis often go hand in hand.

Bone remodeling

Bone remodeling in the adult skeleton serves for a continuous bone replacement [9]. Under optimal conditions, this cellular process keeps bone mass constant from

puberty throughout life. In the current understanding, three major bone cells are involved in this process. All three cell types communicate with each other through the secretion of messengers, while the balance of bone formation and bone resorption is aimed to be well regulated. The bone cells involved in bone remodeling are also the protagonists for fracture healing.

Osteoblasts are bone-forming cells derived from mesenchymal stem cells (Figure 2A). Bone formation is enhanced by vitamin D as well as PTH (Figure 2B).

Osteoclasts are mostly multinucleated and represent the bone-resorbing cells (Figure 2A). Osteoclast

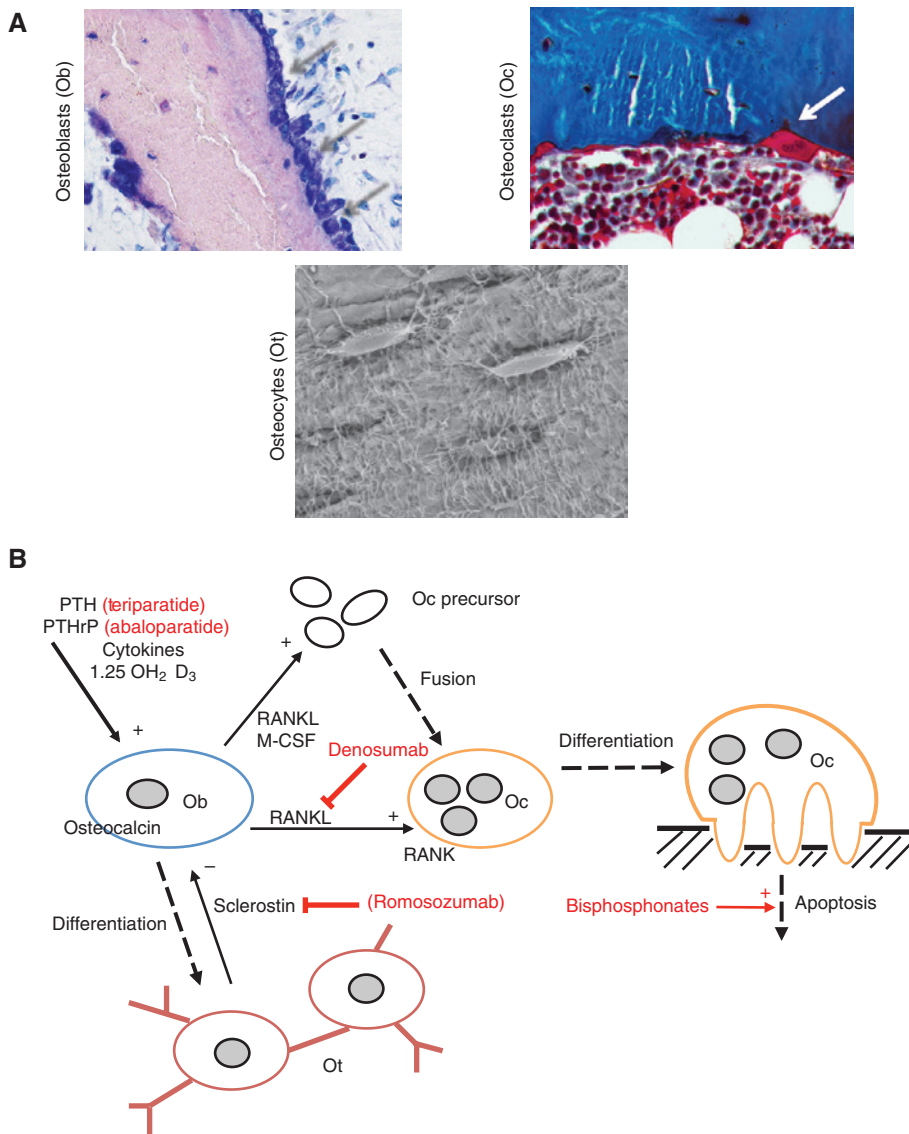


Figure 2: Bone remodeling.

(A) Microscopic views of bone-forming osteoblasts (toluidine blue staining) as well as bone-resorbing osteoclasts (trichrome Goldner staining). Osteocytes (bottom row) are connected via canalicular extensions and are able to sense mechanical strain to signal osteoblasts and osteoclasts. (B) Simplified bone remodeling scheme demonstrates the interplay between the bone cells. Ob, Osteoblasts; Oc, osteoclasts; Ot, osteocytes; (+), stimulation; (-), inhibition. Osteoporosis drugs and their targets are in red.

precursor cells become activated multinucleated osteoclasts through their activation by the receptor activator of nuclear factor- κ B ligand (RANKL) as well as macrophage colony-stimulating factor (M-CSF; Figure 2B).

Osteocytes are cells entrapped in the bone matrix and able to sense mechanical strain (90%–95% of all bone cells) [10]. They originate from osteoblasts, which represent the primary bone-forming cells [11]. Osteocytes are well connected via canaliculi, thereby communicating with each other and the bone surface [12] (Figure 2A). They express several factors that regulate phosphate metabolism [i.e. fibroblast growth factor-23 (FGF-23)], which indicates that they are involved in matrix mineralization. Furthermore, osteocytes produce sclerostin to inhibit the Wnt signaling pathway with subsequent negative influence on bone formation [13]. Interestingly, circulating sclerostin levels have been found to increase with age [14].

In the two bony compartments, trabecular and cortical bone, different physiological and pathophysiological mechanisms have to be differentiated, which also have clinical relevance for osteoporosis treatment [15]. Trabecular bone with its thin plates has a low matrix volume and a large surface area, which is why signaling molecules are thought to have more effects on remodeling. Cortical bone has comparably smaller surfaces but contributes to 80% of the weight of the human skeleton. Especially in long bones, including the femur, cortical bone is found. In aging cortical bone, bone loss from the inner (endocortical) surface exceeds deposition of bone on the outer (periosteal) surface, which leads to bone fragility [16]. Furthermore, the accumulation of microdamage increases and the number of osteocyte lacunae decreases with age in cortical bone, which might jeopardize the skeletal integrity and bone repair in aged cortical bone [17].

Calcium homeostasis

Next to possible imbalances in the cellular bone remodeling process, an intact calcium homeostasis and bone mineralization is essential for fracture prevention and postfracture care. Inadequate calcium supply leads to mineralization defects of the skeleton, whereas calcium homeostasis is highly dependent on vitamin D status [18]. Active vitamin D (1,25-OH₂-D₃) increases intestinal calcium absorption and reduces excessive bone remodeling via direct and indirect pathways, therefore leading to decreased risk of fracture [19]. In Germany, there is an unequivocal endemic vitamin D deficiency affecting 60%–89% of the population according to the Robert

Koch Institute (RKI) [20]. Any vitamin D supplementation should aim 25-OH-D₃ serum levels of more than 30 µg/L (75 nmol/L), as this has been shown to be the threshold to exclude any mineralization defect and osteomalacia [21]. In the histologic observation of bone biopsies, an accumulation of unmineralized bone matrix, called osteoid, covering more than 20% of the bone surface is called osteomalacia (Figure 3A). We have shown previously that osteomalacia affects up to 25% of the assumed-to-be healthy population [21] and that osteomalacia is more common in patients with hip fracture than in patients without hip fracture [22]. Another consequence of vitamin D deficiency is also a secondary hyperparathyroidism, which leads to the subsequent activation of bone resorption with inadequate fracture healing (Figure 3B). Of note, 25-OH-D₃ is the best predictor of vitamin D status and active 1,25-OH₂-D₃ should only be tested in patients with renal failure due to the inadequate activation of 25-OH-D₃ in the kidneys.

Of major importance in the treatment of elderly patients is also hypochlorhydria, which constitutes a deficiency of gastric acid. Impaired gastric acidification negatively affects calcium homeostasis and bone mass [23, 24]. Therefore, the use of proton pump inhibitors (PPIs) is associated with the increased risk of fracture. In fact, a meta-analysis including 1,084,560 patients with 62,210 PPI users demonstrated an increased risk of hip or any-site fractures among PPI users [25]. In the case of fracture, hypochlorhydria leads to increased mobilization of calcium from the skeleton and posttraumatic bone loss, which may be responsible for the increased risk of further fractures after the initial fracture event [26]. Importantly, only calcium citrate and calcium gluconate supplements, which can be ingested independently from gastric acid, are shown to balance calcium homeostasis and increase BMD in patients with hypochlorhydria [27]. If no defective intestinal calcium absorption is present, a nutritional daily calcium intake of 1000–1500 mg calcium should be guaranteed, whereas no additional calcium supplementation is needed. That a balanced interplay of calcium, vitamin D, and PTH is not only crucial to provide a healthy skeleton from the beginning but also for fracture healing is the fact that adequate calcium supply is essential for callus mineralization and the bridging of the fracture gap [26].

Make the first fracture the last – implications for treatment

Closing the gap in between surgical fracture treatment and follow-up examination and therapy is of major

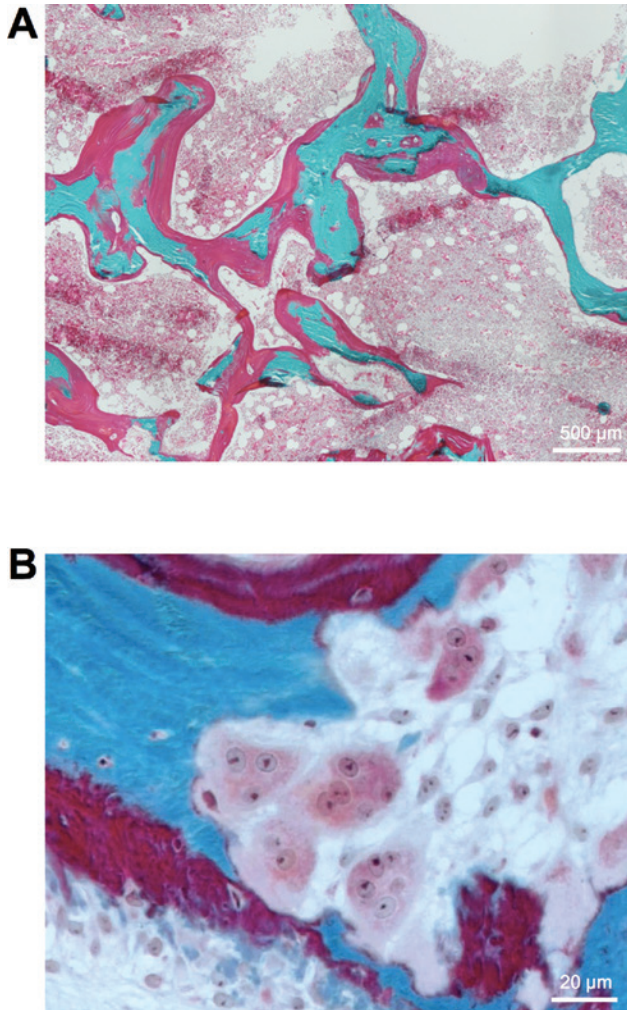


Figure 3: Osteomalacia is an underdiagnosed differential diagnosis of osteoporosis.

(A) A diagnostic iliac crest bone biopsy shows an accumulation of unmineralized bone called osteoidosis. Surface (>20%) and volume (>2%) osteoidosis are the diagnostic hallmarks of osteomalacia. (B) Activated bone resorption in a patient with secondary hyperparathyroidism caused by vitamin D deficiency. Multinucleated osteoclasts can be seen. Trichrome Goldner staining of 5-μm-thick undecalcified sections (green-blue, mineralized bone; red, osteoid).

importance to prevent further fractures. Therefore, any clinician dealing with fractures in elderly patients should initiate the basic osteologic diagnostics. Here, the implementation of coordinator-based fracture liaison services (FLS) in health-care systems has been shown to raise the postfracture assessment rate from 20% to 80%–90% [3].

With regard to the outlined bone remodeling process and possible imbalances in the elderly, a postfracture diagnostic and treatment algorithm should be implemented. After any low traumatic fracture has occurred in patients older than 60 years, basic diagnostics, including detailed medical history, assessment of risk

factors, DXA, and laboratory tests, should be arranged. In the case of low traumatic vertebral or hip fracture and exclusion of secondary causes for osteoporosis, a specific osteological treatment has to be started afterwards. The most commonly used and approved osteoporosis medications in North America and Europe include bisphosphonates (antiresorptive), denosumab (antiresorptive), and teriparatide (osteoanabolic). Of note, any specific therapy requires the normalization of calcium homeostasis.

Nitrogen-containing bisphosphonates (including alendronate, ibandronate, risedronate, and zoledronate) are the oldest and most experienced osteoporosis drugs and have been shown to be highly effective in primary and secondary fracture prevention. They interact with the mevalonate biosynthesis and inhibit the farnesyl pyrophosphate synthase, which eventually leads to the disruption of the cytoskeleton in osteoclasts and subsequent apoptosis. In postmenopausal women with a T-score lower than -2.5 , long-term treatment with alendronate leads to a 50% reduction of nonvertebral fractures [28].

Denosumab, which is a human monoclonal antibody against RANKL, the main regulator of osteoclastogenesis, showed a reduction of new vertebral fractures by 68% and hip fractures by 40% [29]. A main advantage of denosumab, particularly in elderly patients with declining renal function, is that it is not eliminated by the kidneys and therefore also suitable in patients with renal insufficiency [30]. The osteoanabolic drug teriparatide (PTH-1-34) is less commonly used and generally reserved for patients with severe osteoporosis. Its use is furthermore limited to 18–24 months, as the osteoanabolic effect of recombinant PTH is limited to this time called the “anabolic window” [31]. Therefore, the treatment of patients with severe osteoporosis requires the sequential use of several drugs, for example, both teriparatide and denosumab [32]. Switching from teriparatide to denosumab is hereby associated with a continuous increase in BMD. For the action mechanism of these three drugs, see also Figure 2B. A promising drug target is also sclerostin and its inhibition, which is currently subject of clinical trials [33].

The effect of osteoporosis drugs on fracture healing itself is another point that has often been discussed [34] and will only shortly be addressed here. Importantly, there is no evidence for a significant negative effect of bisphosphonates or denosumab on fracture healing in humans. Teriparatide has been shown to accelerate fracture repair in small clinical trials [35], but a further investigation is needed. Therefore, the main focus should lie on the initiation of osteoporosis diagnostics and treatment after fracture, whereas risk factors for nonunion such as

diabetes, nicotine, glucocorticoids, or chemotherapy have to be considered [36].

We conclude that the basic diagnostic procedures (assessment of medical history, DXA, laboratory tests, and HR-pQCT if required) are all relatively easy to carry out. This way, patients suffering from fragility fractures can be diagnosed and the appropriate treatment can be started leading to a significantly decreased risk of further fractures. Our knowledge of bone biology has advanced in the last years, which is why different pathways can be antagonized specifically to stop further bone loss and treat patients with osteoporosis or other skeletal diseases. One has to keep in mind that a balanced vitamin D and calcium homeostasis is the fundament for any further specific therapy.

Author Statement

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Author Contributions

Writing of the manuscript: Tim Rolvien; Michael Amling.

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Supplemental Material: The article (DOI: 10.1515/iss-2016-0025) offers reviewer assessments as supplementary material.

Reviewer Assessment

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Oct 03, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	100
Custom Review Question(s)	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	5 - High/Yes
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	5 - High/Yes
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes
Comments to Author:	
-	

Reviewer 2: Richard Stange

Nov 15, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	N/A
Custom Review Question(s)	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	N/A
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	4
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes
Comments to Author:	
<p>The review article addresses the important topic of age related impairment of bone quality and importance of fragility fracture treatment. The experienced authors provide a good overview of the underlying bone biology in the elderly and the current state of the art of post fracture treatment of bone disorders like osteoporosis, osteomalacia or vitamin D deficiency. The author emphasize the cooperation between the trauma surgeon treating the fracture and the osteologist taking over the after treatment of bone disease. The current state-of-the-art investigation methods are presented and explained regarding their usefulness with regards to the underlying pathology. The authors postulate an enhanced effort in order to overcome the current undertreatment of bone diseases in the elderly with fragility fractures.</p> <p>The article gives a good overview of the increasing problem of age-related fragility fracture and the insufficiency of after treatment of underlying bone diseases. It reflects and summarizes the current literature about this topic and gives advice for the treatment of those patients.</p> <p>For clinical application and daily work, some additional practical implications for the management of patients with fragility fracture or the mentioned fracture liaison service might be helpful and could be added.</p>	