Review Article

The Effect of Osteoporosis on the Pathogenesis and Healing of Distal Radius Fragility Fractures

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Abstract

Osteoporosis is a significant predisposing factor for fragility fractures of the distal radius. The disorder is characterized by a significant and long-standing imbalance between bone formation and absorption, resulting in a gradual reduction in bone mass that worsens with age. This narrative review aims to present recent data regarding the effect of osteoporosis on the pathogenesis and healing of distal radius fragility fractures. Although research on this topic is limited, current studies suggest that during the osteopenia or osteoporosis stage, both trabecular and cortical bone undergo quantitative and qualitative changes. As a result, a weak cortex shell surrounds the trabecular bone compartment which exhibits significant deterioration of its microarchitecture, with cortical bone being the most critical factor in resisting distal radius fractures in the early stages of osteopenia. Concerning fracture healing, and based on limited published data, it is believed that osteoporosis does not have a significant impact on the progression of fracture healing in distal radius fractures, although there appears to be a tendency towards a potential negative effect. The treating physician must consider the unique characteristics of osteoporotic bone, including reduced healing ability and relatively lower functional requirements of patients. Balancing these factors is crucial in determining an appropriate treatment plan.

Keywords: Distal radius fracture, Osteoporosis, Pathogenesis, Healing

Introduction

Osteoporosis is a chronic metabolic disease characterised by low bone mass and deterioration of bone tissue, leading to disruption of its microarchitecture. This condition can significantly reduce bone strength, increasing the likelihood of fractures. The incidence of osteoporosis has been on the rise in recent decades, leading to a corresponding increase in the occurrence of fragility fractures. These fractures are caused by low-energy injuries and trauma, such as falls from standing height or lower. In the United States, the annual incidence of fragility fractures has been around 2 million, with projections suggesting an increase to 3 million by the end of 2025. The healthcare cost associated with these fractures is expected to skyrocket to $25 billion per year.

In orthopedic trauma settings, the distal radius fractures (DRFs) account for 18% of all fractures in older adults, making it the second most frequently occurring type of fractures, with hip fractures ranking first. Unlike hip fractures, which are accompanied by high mortality (20%) and disability (50%) rates, DRFs make it difficult for patients to carry out their daily activities but do not seem to increase their overall mortality. However, this type of fracture is characterized by an increased risk of new fragility fractures occurring in the coming years. Older adults who have sustained a fragility fracture have an 11% risk of subsequent fractures in the next three years, but patients with a DRF have a fivefold increased risk of suffering a hip fracture in the upcoming year. While the outcome of a DRF is generally considered...
more favorable than that of a hip fracture, it is also a warning sign for the potential occurrence of new fragility fractures that can significantly increase morbidity or even mortality in patients.

This narrative literature review aims to present recent research findings concerning the impact of osteoporosis on the pathogenesis and healing of fragility fractures in the distal radius.

**Materials and Methods**

A comprehensive literature search was conducted to identify relevant studies for inclusion in this narrative review on the effect of osteoporosis on the pathogenesis and healing of distal radius fragility fractures. Electronic databases, including PubMed, Scopus, and Embase, were searched using appropriate keywords and search terms such as “osteoporosis”, “distal radius fractures”, “fragility fractures”, “pathogenesis”, and “healing”. The search was limited to English articles published between January 2005 and February 2023. Inclusion criteria encompassed studies that examined the relationship between osteoporosis and distal radius fragility fractures, including clinical studies, observational studies, cohort studies, case-control studies, and review articles. Exclusion criteria included non-English studies and studies that focused solely on other types of fractures or did not specifically address the pathogenesis or healing of distal radius fragility fractures.

Following the initial database searches and removal of duplicates, the titles and abstracts of the remaining articles were screened. Full-text versions of relevant articles were retrieved and evaluated against the predefined inclusion and exclusion criteria. Additionally, the reference lists of included studies were screened to ensure no relevant articles were missed.

**Results**

The initial search yielded a total of 907 articles, and after removing the duplicates and applying the inclusion and exclusion criteria, 29 articles were selected for this review.

**Osteoporosis and Pathogenesis of distal radius fragility fractures**

Osteoporosis is one of the most crucial predisposing factors for the occurrence of a fragility fracture of the distal radius and should always be considered by treating physicians. The significant and long-standing imbalance between bone tissue formation and absorption that characterizes the disorder results in a gradual reduction of bone mass, which worsens with increasing age of the patient. There are four main factors that predispose the older adults to osteoporosis: 1) Hormonal changes, 2) Decreased physical activity, 3) Calcium deficiency, and 4) Vitamin D deficiency. Several studies, including clinical and experimental ones, have demonstrated significant differences between the normal and osteoporotic distal end of the radius, both in terms of structural and biomechanical properties. Spadaro et al., in a cadaveric study of 21 fresh forearm cadavers, found that the bone mineral content and bone mineral density were the most significant factors correlating with the strength of the distal radius. They also found a correlation between trabecular bone density and bone strength, indicating that the strength of the distal radius is primarily determined by the quality of trabecular bone and the quantity of cortical bone. More recent in vivo studies have shown that significant changes in the structure and biomechanical properties of the distal radius occur with age. Kawaiilak et al. (2014) demonstrated in 51 women that osteoporosis is related to a combination of loss of trabeculae and a simultaneous increase in trabecular size, along with a reduction in cortical content, density, and thickness. In the same year, Stein et al. (2014) found that among 117 postmenopausal women with osteopenia, those who sustained a distal radius fracture (DRF) had lower cortical and trabecular volumetric bone mineral density, a different trabecular structure that was separated, thinner, and rod-like, reduced trabecular connectivity, and statistically significant lower stiffness of their distal radius compared to the control group who did not sustain a fragility fracture. Bala et al. (2014) attempted to reconcile these findings and concluded that the deterioration of cortical microarchitecture is a statistically significant independent factor for fracture risk in osteoporotic and osteopenic women. It is precisely this microarchitecture of the cortical bone – which is characterized by the term “cortical porosity” – and especially the network of vascular canals that has been studied in recent years in relation to its influence on the occurrence of DRFs. Bjornerem et al. (2013) showed that an increase of one standard deviation in the cortical porosity of the distal radius is related to an increased fracture risk, odds that are even greater for the distal tibia and distal fibula.

Rozental et al. (2008), in a retrospective study of 298 patients who sustained a fragility DRF, found that only 21.3% of them had undergone a bone mineral density examination prior to the injury, and 57% were found to have osteopenia. Additionally, the authors found that patients who had undergone a bone mineral density examination were 2.5 times more likely to receive an anti-osteoporotic treatment, potentially preventing future fractures.

In most cases, fragility DRFs are caused when a patient falls while standing or walking and lands on their outstretched hand. Reduced bone mineral density in the area results in the bone’s inability to withstand the deforming forces exerted during the fall, leading to a significant increase in the frequency of these fractures. Furthermore, this specific weakness in the bone results in a characteristic appearance of fragility fractures, with greater degrees of displacement, angulation, and comminution of the bone fragments.
Lill et al. (2003) conducted a radiologic and biomechanical study on 118 intact forearms from older adult donors, which were subjected to simulation of a fall on the outstretched hand. The study found a direct correlation between the severity of the fracture and the reduced quality of the bone in the area, with the highest degree of correlation observed in relation to the cortical area and trabecular density. Additionally, the study revealed that the severity of fragility fractures was underestimated in several cases by plain radiological examination, leading to potential difficulties in successful treatment. The study suggests that osteoporosis can result in early or late loss of bone fragment position, resulting in malunion, non-union, and the subsequent need for open reduction and internal fixation.

Clayton et al. (2009) conducted a prospective study to investigate the relationship between the degree of osteoporosis and the severity of DRFs in 137 older adult patients. The main findings of the study are summarized below:

- Osteoporosis was associated with a 43% probability of early instability of the bone fragments, 39% of late carpal malalignment, and ultimately 66% of malunion.
- The corresponding percentages for patients with osteopenia were 35% for early instability, 31% for late carpal malalignment, and 56% for malunion.
- Finally, in patients with normal bone mineral density of the femoral neck, the corresponding percentages were 28%, 25%, and 48%, respectively.

These findings demonstrate a direct correlation between the degree of osteoporosis and the severity of DRFs. This correlation is not only radiologically significant, but also clinically relevant since instability may require surgical intervention, carpal malalignment is associated with significant deterioration of the function of the wrist and hand joints, and malunion, although it may be expected to some degree in this age group, is almost always associated with varying degrees of functional deficits.

In an interesting study, Itoh et al. (2004) investigated the impact of bone mineral density reduction rates in the distal third (R3) and tenth (R10) of the radius and ulna (U3 and U10) on the incidence, severity, and complications of DRFs. The main findings of the study were that:

1. Reduction of bone mineral density in the R3 and R10 areas can reliably predict subsequent distal radius fractures in women over 80 years old, while reduction of bone mineral density in the U3 and U10 areas can predict ulnar styloid fractures in women aged 50-59 years.
2. Reduction of bone mineral density in the R10 area is a reliable predictor of displacement and loss of reduction of fracture fragments after initial close reduction and wrist immobilization.

These findings suggest that monitoring bone mineral density in specific areas of the radius and ulna can help predict the risk of DRFs and potential complications, allowing for more targeted preventive measures and treatment options.

Although scientific research on DRFs has long focused exclusively on postmenopausal women, recent years have seen an increase in studies examining the mechanisms of their pathogenesis in older adult men. In the first relevant study, known as the “Mr F study,” Hanusch et al. (2017) examined 61 male patients with fragility fractures of the distal radius and concluded that, compared to the control group, men with a fracture had a statistically significant lower bone mineral density in the ultradistal radius area of both their dominant and non-dominant forearm. Based on these findings, the authors suggested that all men who have suffered a fracture of the distal radius after low-energy trauma should be considered candidates for future fragility fractures.

In conclusion, from the studies discussed above, it is clear that osteopenia and osteoporosis result in significant alterations to the structure and biomechanical properties of the distal radius, rendering this region of the skeleton particularly susceptible to fragility fractures even with minimal trauma. Another important finding is that, at least in the early stages of osteopenia, cortical bone is the most important factor resisting distal radius fractures compared to trabecular bone.

**Osteoporosis and healing of distal radius fragility fractures**

Fracture healing is a complex and gradual process that occurs at both the molecular and cellular levels and can be classified into two types: direct/primary healing, which occurs after open reduction and rigid internal fixation and stabilization of the bone fragments, and indirect/secondary healing, which occurs when micro-movements at the fracture site are permitted. The indirect healing process consists of four stages: the inflammatory stage, the formation of soft callus, the formation of hard callus, and finally, the bone remodeling stage. This intricate process involves a number of biological and mechanical factors that are negatively affected by osteoporosis, as multiple studies have shown. Osteoporosis can impact the healing of distal radius fractures at two levels: 1) by potentially modulating the natural course of the fracture healing process, and 2) by affecting the treatment plan.

The natural course of the healing process

It appears that following an osteoporotic fragility fracture, the total bone mass in the fracture site is reduced after the completion of the healing process, along with a decrease in the mechanical strength of the newly formed bone. The healing process itself is delayed, primarily due to slower callus mineralization. According to Cheung et al. (2016), fracture healing of an osteoporotic bone can be delayed due to various factors, including 1) decreased levels of local angiogenesis, 2) decreased levels...
of recruitment and differentiation of mesenchymal stem cells, especially during the early stages of bone healing, 3) delayed expression of the estrogen receptor, due to different sensitivity between osteoporotic and healthy bones, 4) impairment of the differentiation of osteoblasts and chondrocytes, and 5) a number of factors related to angiogenesis that affect vascular invasion along with the degradation of cartilaginous matrices. All of the above factors negatively affect not only the speed of healing and the quality of the newly formed bone but also the capacity of callus remodeling during the fourth stage of the fracture healing process.\textsuperscript{23} Thormann et al. (2014)\textsuperscript{24} provided one of the first experimental proofs of the above in an experimental model in female Sprague-Dawley rats who underwent metaphyseal osteotomy, showing that the osteoporotic group 1) had decreased shear rigidity, 2) the callus formed six weeks after the osteotomy and the non-compressive plate-screw fixation had a larger volume of unmineralized tissue, and 3) no signs of a remodeling process were observed, unlike the experimental animals in the control group.

The small number of research studies related to this topic is illustrated in the systematic review by Gorter et al. (2021)\textsuperscript{25}, which examined the impact of osteoporosis and its treatment on fracture healing. The review included studies in both humans and animals; of the 23 studies isolated regarding the effect of osteoporosis on the healing of fractures, only five were clinical studies involving humans, including one study on fractures of the femoral shaft, one on subcapital humeral and distal radial fractures\textsuperscript{26}, and three on various fracture sites of the human body\textsuperscript{28-30}. The main findings of this systematic review can be summarized as follows:

- In animal models, osteoporosis was related to decreased bone growth and callus formation, decreased biomechanical strength, and delayed cellular differentiation during the fracture healing process.
- Large databases in humans related osteoporosis as a risk factor for fracture non-union, whereas another found a prolonged fracture healing time.
- In animal models, anti-osteoporotic medication showed inconsistent results on fracture healing.
- In humans, there is no evidence of a positive effect on fracture healing for bisphosphonates, whereas parathyroid hormone seems to reduce the healing time in hip fractures.

Regarding distal radius fractures, most relevant studies have been conducted on animal models. In humans, however, Meyer et al. (2014)\textsuperscript{31} investigated 18 patients with wrist fractures and found that 12 weeks after injury, lower values of the Patient Rated Wrist Evaluation (PRWE) questionnaire\textsuperscript{32}, which indicates better final outcomes of the injury, were significantly associated with increased bone mineral density of the trabecular bone in the area. According to the authors, osteoporosis is a crucial factor that determines the final outcome of distal radius fractures in terms of functionality, joint range of motion, and pain level for at least 12 weeks after the injury.

Gorter et al. (2020)\textsuperscript{27} conducted a retrospective cohort study to investigate the impact of osteoporosis on the healing of wrist and subcapital humeral head fractures. A total of 311 patients with distal radius fractures were evaluated for delayed or non-union. Although patients without osteoporosis had more favorable fracture healing progression, the study did not have sufficient statistical power to reach a definitive conclusion. The authors suggest that given the high prevalence of osteoporosis in both female and male populations aged over 50 years and the potential adverse effects of a fractured distal radius on individuals’ functionality, further research in this area is necessary.

How osteoporosis affects the fracture treatment regimen

The therapeutic treatment of distal radius fractures in older adult osteoporotic patients is still controversial. For many decades, guidelines have been focused on relatively young patients with healthy bones\textsuperscript{33}. According to Tulipan et al. (2015)\textsuperscript{30}, the main considerations when treating a patient with a fragility distal radius fracture are:

1. Taking into account the patient’s needs and requirements in relation to activities of daily living.
2. Treating osteoporosis comprehensively, not just the fracture itself, to prevent subsequent fragility fractures, which have a particularly high risk of occurrence\textsuperscript{6}.
3. If surgery is required, the orthopaedic surgeon should consider not only the type of fracture but also the poor quality of the bone to achieve optimal open reduction and internal fixation.

Regardless of the treatment approach, an osteoporotic distal radius fracture presents significant challenges for the orthopaedic surgeon. Reduced bone strength, particularly in the metaphyseal or meta-diaphyseal region, can result in comminuted and/or unstable fracture types, small bone fragments in the epiphyseal region that make osteosynthesis difficult, unstable or on the contrary, very rigid fixation causing delays in fracture healing, diminished holding power of osteosynthesis screws, and early implant fatigue, leading to loosening and ultimately failure of the osteosynthesis\textsuperscript{34}. In this field, notable are the results of a comprehensive systematic literature review examining the outcomes and complications of treating unstable DRFs in older adult patients\textsuperscript{35}. The authors analyzed 21 relevant papers and found that, although conservative treatment with cast immobilization produced worse radiographic findings compared to the surgical treatment group (particularly ulnar variance and volar tilt), there were no statistically significant differences in terms of final functional outcomes. The authors suggest that further research comparing invasive and potentially more costly treatment methods with conservative treatment should be conducted before broader adoption of the former for patients in this population\textsuperscript{35}.\textsuperscript{36}
Conclusion

Fractures of the distal radius in osteoporotic patients represent a unique category of fragility fractures with distinct clinical and pathophysiological features, which present a significant challenge to treating physicians. Despite the large and increasing number of patients who suffer from these fractures, this narrative literature review revealed a paucity of published original research studies, particularly on the healing characteristics of these fractures. In contrast, there are relatively more in vitro experimental studies investigating their pathogenesis, which indicate that osteopenic or osteoporotic bone undergoes quantitative and qualitative changes in both trabecular and cortical bone, resulting in a weakened cortex shell surrounding a less dense trabecular matrix.

Although the biological characteristics of the healing process of these unique fragility fractures are not fully understood, it appears that during the acute healing phase, the mechanical properties of the injured site are weakened. The callus formed is less mineralized and has decreased stiffness compared to the callus produced by normal, non-osteoporotic bone. Additionally, the remodelling process is characteristically incomplete. It seems that, at least in the early stages of osteopenia, cortical bone plays a more critical role in resisting distal radius fractures compared to trabecular bone.

Regarding treatment, research data is even scarcer, with very few high-quality clinical studies available. The development and use of locking plates have allowed for safe fixation of osteoporotic bone without the need for bicortical screws. Despite the radiographic superiority of the final result after surgical treatment, there is no definite difference in functional outcomes compared to conservative treatment. Nonetheless, treating physicians must consider the unique characteristics of osteoporotic bone and strike a balance between the reduced bone healing ability and the relatively reduced functional requirements of patients.

References


