ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Review Article

Osteoporosis and Fractures: Less Known or Overlooked Aspects

Rosini Sergio[1], Molfetta Francesco[2], Rosini Stefano[3], Palermo Augusto[4] and Molfetta Luigi[5]*

[1]*Biomaterial Research Center, Livorno, Italy*

[2]*DINOGMI Department, School of Medical and Pharmaceutical Sciences, University of Genoa, Genoa, Italy*

[3]*Smile-Restyle, Livorno, Italy*

[4]*Head Prosthetic Surgery Unit, Istituto Clinico Humanitas Bergamo Gavazzeni, Bergamo, Italy*

[5]*DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, University of Genoa, Genoa, Italy*

***Corresponding Author:** Molfetta Luigi, Professor, DISC Department, School of Medical and Pharmaceutical Sciences, Research Center of Osteoporosis and Osteoarticular Pathologies, University of Genoa, Genoa, Italy.

Received: January 23, 2026; **Published:** February 05, 2026

Abstract

Osteoporosis is a multifactorial skeletal disorder traditionally explained by the estrogen-deficiency model. However, recent evidence indicates that bone loss begins earlier than menopause and is influenced by multiple age-related mechanisms beyond hormonal decline. Objective of the paper is to highlight less recognized determinants of osteoporosis and fragility fractures, focusing on bone aging, oxidative stress, and early trabecular bone loss independent of bone mineral density (BMD). Early trabecular and cortical bone loss has been observed in both men and women before the onset of sex hormone deficiency. Senescence-related alterations and accumulation of reactive oxygen species (ROS), advanced glycation end products (AGEs), and advanced oxidation protein products (AOPPs) emerge as central mechanisms of skeletal deterioration.

Keywords: *Osteoporosis; Fracture; Old Age*

Introduction

It has now been about 50 years since we first began speaking of "osteoporosis" as a serious condition affecting bone structure, increasing the risk of fragility fractures. The responsibility for this alteration has been attributed to numerous factors or conditions, including the use of certain drugs, deficiencies of substances considered essential for bone health, physical inactivity, genetic alterations, but the most significant cause in the past was attributed to the loss or decline of sex hormones. This led to the formulation of the estrogen-centric theory underlying osteoporotic pathology, together with the inevitable bone decline linked to aging [1].

More recently, these aspects have been further clarified, and it is now recognized that aging per se does not represent the disease, but rather one of several factors responsible for the deterioration of bone structure and tissues, predisposing the skeleton to fragility fractures. Indeed, strong evidence for a pivotal contribution of aging to fractures, independent of bone mass, had already been observed and reported in the study by S.L. Hui., *et al.* (1988), which clearly demonstrated that, even with equal BMD, a 20-year increase in age is accompanied by a fourfold increase in fracture risk [2]. It is due to Riggs BL and others (2008) that it was identified how, beyond sex

hormone deficiency, bone mineral density loss occurs even before the consequences of such hormone deficiency manifest [3]. However, it can be assumed that with advancing age, the effects of senile decline and hormonal loss add to other less apparent but equally decisive events.

Riggs reported that in both men and women there is a constant loss of both trabecular and cortical bone, more evident in women, already in the perimenopausal period, but which intensifies at all levels after the age of 50, especially for cortical bone.

A less evident loss is also observed in men, particularly in lumbar trabecular bone. Data from the study indicate that in women there is a loss of 37% of trabecular bone before age 50, and 6% of cortical bone. Similar values are reported for men. It is evident that the early loss of trabecular bone, and-though to a lesser extent-cortical bone, already in young individuals at an age when plasma concentrations of sex hormones are usually adequate, indicates that there must be other conditions responsible for the continuous bone reductions, different from those characterizing senile osteoporosis. Among the possible causes, a premature reduction of sex hormones in women has been reported, as occurs in cases of premenopausal oophorectomy.

A study by Slemenda C., *et al*. (1996) [4] conducted in women aged 32 to 77 years reported that bone mass in women was negatively associated with sex hormone-binding globulin (SHBG) concentrations, while bone loss became evident in peri- and post-menopause. Premenopausal women showed bone loss only from the hip (-0.3%/year), but positive values in the radius and spine. Bone loss was significantly associated with lower androgen concentrations in premenopausal women and with lower estrogen and androgen levels in peri- and postmenopausal women. The authors concluded that sex steroids are important before menopause and for a period up to 20 - 25 years after.

Cortical bone loss occurs around menopause and progresses fairly linearly thereafter, clearly dependent on estrogen reduction. The authors suggested that both estrogens and androgens play important roles in skeletal health. However, regarding premenopausal bone loss, these effects are limited to androgens and are relatively modest.

In the perimenopausal period and afterwards, estrogens and androgens act independently to slow bone loss. SHBG is consistently negatively associated with BMD, but not with bone loss. The mechanism of this effect is unknown and may reflect processes occurring at earlier ages. A paper of V. Seifert-Klauss., *et al.* (2012) [5] reports that women in the menopausal transition lose trabecular bone at a rapid rate despite intermittently high and usually normal estrogen levels. This prospective study documents trabecular bone changes in women through the entire perimenopause, which may last up to 10 years.

The onset of trabecular bone loss already in youth, at the end of skeletal development, compels us to identify possible endogenous or exogenous factors responsible for this premature loss in order to evaluate potential preventive therapies. It is logical to consider that, at a certain stage of life, the effects of "bone aging" also begin to affect skeletal health, contributing alongside hormonal decline.

Senile decline and mechanistic insights

It is now demonstrated that the effects of senile decline are due to altered differentiation of BMSCs, which tend toward an adipocytic rather than osteoblastic phenotype, resulting in a reduced number of these cells and decreased bone formation [6,7]. Among the reasons for altered BMSC differentiation, telomere shortening, oxidative stress, and various genetic and epigenetic regulatory elements have been reported [8]. However, there are also age-related changes in bone itself that contribute to the increased fracture risk for the same BMD, including deterioration of collagen and non-collagen proteins, changes in mineral and water content, accumulation of advanced glycation end products (AGEs) and ROS [9]. Other considerations also deserve attention in order to identify those factors responsible for bone structure deterioration independent of BMD. For example, fractures at one skeletal site increase the risk of further fractures at other sites; moreover, despite treatment with antiresorptive drugs, only part of the reduction in subsequent fractures can be attributed to an

increase in bone mass. Third, many genetic effects on bone strength are mediated by factors other than bone mass, such as altered bone architecture, delayed microfracture repair, excessive bone turnover, or inadequate attainment of peak bone mass in youth.

The loss traumatic or apoptotic of osteocytes also makes an independent contribution to bone strength, as they allow more efficient repair of microfractures and help preserve bone hydration. Taken together, the theory attributing bone loss with advancing age primarily, or even exclusively, to estrogen decline or general hormonal collapse appears incomplete. It is evident that other changes act as co-factors, such as excess glucocorticoids, progressive renal decline, latent intestinal malabsorption of calcium or vitamin D, in addition to events linked to senility. Recent studies [10] have reported that age-related accumulation of Advanced Oxidation Protein Products (AOPPs) accelerates bone deterioration by increasing resorptive activity and decreasing bone formation, as a consequence of increased intracellular oxidative stress (OS) due to ROS accumulation and upregulation of sclerostin. In addition to the evidence that OS is a pathogenetic element in age-related bone loss, it has also been reported that the protective effect of estrogens on bone mass is partly due to their ability to protect cells from OS [11].

Discussion

With aging, the well-known problems emerge not only in bone tissue structure but also in muscles: fragility, loss of strength, and, in general, reduced regenerative capacity. Naturally, attempts have been made to explore the possibility of rejuvenating tissues or their cells. This possibility has been evaluated for muscle tissue as well as for bone cells, which, despite having different lifespans, also tend to age, undergo apoptosis, or die, with limited regenerative potential. For a long time, bone degeneration was attributed to osteoporosis, which manifests particularly when defenses linked to sufficient concentrations of estrogens and androgens decline.

However, despite the importance of these hormonal factors, more recent mechanistic studies have highlighted that, beyond aging, the most decisive risk factor is the increase in reactive oxygen species (ROS), given their negative impact on the formation and vitality of bone cells: osteoblasts (OBs), osteoclasts (OCs), and osteocytes (OCys) [12]. Hormone loss tends to reduce defenses against oxidative stress in bone and to increase resorption. With advancing age, increased glucocorticoid production further reduces skeletal hydration, thereby increasing fragility [13].

Thus, it is clear that age-related mechanistic events and oxidative stress are key drivers of bone structure deterioration. Indeed, the reduced production of sex hormones is only one of the risk factors for osteoporosis, and it has been well demonstrated that a reduction in BMD occurs already after the attainment of peak bone mass, well before sex hormone decline. Importantly, fractures themselves are independent risk factors for subsequent fractures, highlighting the role of impaired bone quality beyond BMD alone.

Conclusion

The data presented above show that age-related bone mass decline is independent of steroid status, and osteoporosis represents one of the risk factors predisposing to fractures. The study by Hui (1988) clearly shows that, for the same BMD value, a 20-year increase in age results in a fourfold increase in fracture risk. Obviously, several other risk factors also exist. Is the formation of ROS and oxidative stress therefore the true and main determinant of tissue aging and, ultimately, of human aging? This conclusion is not entirely unfounded and reflects theories already expressed by Harman D. in 1956, later revisited and confirmed by many authors who postulated that intracellular ROS production is the major determinant of human lifespan [14]. This concept was further elaborated by Chien KR., *et al*. (2005) [15], who showed that mitochondrial DNA mutations lead to dysfunction with increased ROS production, which in turn induces further mitochondrial DNA mutations. In this way, progressive developments of age-related phenotypes occur. It is now widely confirmed that bone mass begins to decline after its peak around 25 - 30 years of age, well before the reduction in sex hormones. Nonetheless, this latter event strongly influences skeletal homeostasis by accelerating the loss of bone mass already depleted by advancing age and other factors contributing to fracture risk.

We may therefore conclude that any therapeutic prevention, even the most accurate and best suited to maintain wide functional homeostasis, can only slow down or mitigate the negative effects of the inevitable stress induced by free radicals. The challenge for future research will be to develop targeted strategies capable of modulating oxidative stress and preserving skeletal integrity across the lifespan.

Bibliography

1. Vincenzo Rochira., *et al*. "The endocrine role of estrogens on human male skeleton". *International Journal of Endocrinology* (2015): 165215.
2. Hui SL., *et al*. "Age and bone mass as predictors of fracture in a prospective study". *Journal of Clinical Investigation* 81.6 (1988): 1804-1809.
3. Riggs BL., *et al*. "Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women". *Osteoporosis International* 19.9 (2008): 1323-1330.
4. Slemenda C., *et al*. "Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri-, and postmenopausal women". *Journal of Clinical Investigation* 97.1 (1996): 14-21.
5. Seifert-Klauss V., *et al*. "Bone loss in premenopausal, perimenopausal and postmenopausal women: results of a prospective observational study over 9 years". *Climacteric* 15.5 (2012): 433-440.
6. Jeffrey Kiernan., *et al*. "Concise review: Musculoskeletal stem cells to treat age-related osteoporosis". *Stem Cells Translational Medicine* 6.10 (2017): 1930-1939.
7. Patrick Coipeau., *et al*. "Impaired differentiation potential of human trabecular bone mesenchymal stromal cells from elderly patients". *Citotherapy* 11.5 (2009): 584-594.
8. He L., *et al*. "A shorter telomere is the key factor in preventing cultured human mesenchymal stem cells from senescence escape". *Histochemistry and Cell Biology* 142.3 (2014): 257-267.
9. Bowen Wang and Deepak Vashishth. "Advanced glycation and glycoxidation end products in bone". *Bone* 176 (2023): 116880.
10. Zeng J., *et al*. "Advanced oxidation protein products aggravate age-related bone loss by increasing sclerostin expression in osteocytes via ROS-dependent downregulation of Sirt1". *International Journal of Molecular Medicine* 47.6 (2021): 108.
11. Mohamad NV., *et al*. "Are oxidative stress and inflammation mediators of bone loss due to estrogen deficiency? a review of current evidence". *Endocrine, Metabolic and Immune Disorders - Drug Targets* 20.9 (2020): 1478-1487.
12. Manolagas SC. "From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis". *Endocrine Reviews* 31.3 (2010): 266-300.
13. Weinstein RS., *et al*. "Endogenous glucocorticoids decrease skeletal angiogenesis, vascularity, hydration, and strength in aged mice". *Aging Cell* 9.2 (2010): 147-161.
14. Balaban RS., *et al*. "Mitochondria, oxidants, and aging". *Cell* 120.4 (2005): 483-495.
15. Chien KR and Karsenty G. "Longevity and lineages: toward the integrative biology of degenerative diseases in heart, muscle, and bone". *Cell* 120.4 (2005): 533-544.

Volume 17 Issue 2 February 2026