Chapter

Study on the Impact of Diseases and Medical Treatments on Bone Mineral Density

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Abstract

Several diseases and medical treatments have been found to affect bone quality over decades. Bone mass characteristics summarized in bone mineral density (BMD), geometry, microarchitecture, and mechanical properties are the main parameters permitting to assess the quality of bone. Clinically, the diagnosis of bone diseases and the prediction of bone fracture are largely based on the BMD values. Thus, the investigation of how diseases and treatments alter the BMD value is primordial to anticipate additional treatment for the patient. In this chapter, we summarize the main research studies investigating diseases and treatments' effects on bone quality and more specifically on BMD.

Keywords: bone mineral density, osteoporosis, bone diseases, medical treatments, bone remodeling

1. Introduction

Bone quality depends on the structural and material properties of the bone. By increased mortality and healthcare costs due to bone fractures, bone fragility becomes a major health concern [1]. In order to assess bone fragility, the integration of quantity, quality, and turnover of bone factors is necessary. The BMD, quantified using the clinical imaging technique called X-ray radiography, namely, the dual-energy X-ray absorptiometry (DXA), is one of the most important bone factors reflecting the quality of bone in terms of quantity to assess bone fracture risk in osteoporotic patients [2]. Osteoporosis is a biochemical problem characterized by a decrease in bone mass, a deterioration and an alteration of bone tissue microarchitecture, which increases the risk of fractures. Old bone fracture, oxidative stress, age, and menopause are among the main causes of osteoporosis. Giving its various causes, osteoporosis could affect any gender at any age. For women and men, for example, osteoporosis is associated with aging and more specifically, for women, with hormonal deficiency caused by menopause [3]. Meanwhile for children, BMD loss is generally related to diseases' or treatments' use.

A wide variety of diseases and treatments containing toxic agents for bone cause or contribute to osteoporosis development [4]. In this chapter, we will discuss the diseases and treatments inducing BMD abnormal loss or gain and report different studies' findings concerning diseases and treatment association with osteoporosis. Our work would be subdivided into three main parts: (i) BMD generalities; (ii) osteoporosis in women, men, and children; and (iii) diseases and clinical interventions to limit osteoporosis development.

2. BMD overview

2.1 Bone mineral density

Bone mineral density is the most-used parameter for the prediction of fracture risk in adults. According to the World Health Organization (WHO), bone could be subdivided into four groups based on the BMD values' variation. BMD values are obtained based on DXA images. Based on the calculation of T-score, which represents the number of standard deviation (SD) between studied BMD value and the average value of normal bone of adults of the same sex, the quality of bone can be determined. As far as adults are considered, there are some categories that are more susceptible to get osteoporosis than others; hence, physicians highly recommend them to undergo frequent BMD screenings. By way of illustration, we mention men above 50 years of age who have a historical fracture [5–8], women over 65 years of age, and sometimes the younger women who have an elevated risk of fracture [9]. Based on the fact that osteoporosis is a silent disease and since fragile bones are not painful until the occurrence of fracture, an early screening is always beneficial to detect this disease emergence [10].

For adults, a normal BMD value can be easily determined relative to a specific population. Nevertheless, BMD's use remains difficult for children because of the variation of their bone density and structure during growth. Generally, in this period, bone size and mass grow to reach 90% of the peak bone mass at 18 years of age [11]. Therefore, researchers cannot find a particular normal BMD value to evaluate the bone mineral density levels. In addition to age for children, several variables can also influence the BMD normal value, such as gender, body size, pubertal stage, skeletal maturation, and ethnicity [12]. All these limitations make a diagnosis of osteoporosis more complex [13].

2.2 Dual energy X-ray absorptiometry

DXA imaging technic consists of sending x-rays through the human body, which allows the creation of interior body images based upon the variations of material absorption. Among the many advantages of this technic, we can note its short scanning time, its low radiation dose, and its low cost compared to other imaging technics. DXA provides 2D images of the scanned bone, which can help to extract areal bone mineral density (aBMD) in addition to the hip fracture index (HFRI), and to create a 2D model of the zone of interest, which can be used during finite element modeling. DXA-based finite element models arrive to some extent to determine bone strength and bone behavior vis à vis the mechanical loads. According to [14], DXA-based FE models permit to provide up to 74–77% of experimental femoral strength results. However, despite its advantages, DXA has a poor resolution of images, reducing their

quality, which makes the distinction between cortical and trabecular bone impossible. Moreover, DXA 2D images avoid bone structure, which affects the accuracy of obtained a BMD values.

3. Osteoporosis associated BMD alteration

Every human being is susceptible to develop osteoporosis especially by living long. The maximum humans' BMD is reached by 20 years of age; then, it starts decreasing naturally and gradually by approximatively 1%/year. The rate of this decrease variates depending on gender and can be accelerated by the use of steroid, lack of calcium and vitamin D, smoking, high alcohol consumption, and cancer treatments [15].

3.1 Osteoporosis in women

Majority of osteoporosis patients are women because of menopause. During the menopausal transition period, levels of estrogen drop, causing a big disruption in the bone remodeling process. This process is a biological event permitting to renew the old bone matrix by resorbing the old one and replacing it with a new one. Specific bone cells are involved in this process, where their behavior is controlled by numerous biochemical substances, including estrogen. Indeed, estrogen stimulates bone formation and inhibits bone resorption; thus, by its drop, bone resorption rate becomes higher, inducing bone loss. Based on this fact, other factors related to hormonal disturbance also induce osteoporosis. For instance, the problem of oligomenorrhea and taking high doses of glucocorticoids may cause the declination of bone density and increase the fracture risk for women [16, 17]. The assessment of osteoporosis in premenopausal women is not based on BMD value alone because of its high dependency to age. Therefore, there are other signs beyond BMD value, like the exposure of glucocorticoid, parathyroidism, hypogonadism, and eating disorder [18], which make osteoporosis diagnosis easier. Moreover, fractures' occurrence in this period can be also an index of postmenopausal osteoporosis in women [19].

3.2 Osteoporosis in men

In contrary to women, the cause of osteoporosis in men is unknown. However, many studies have associated this disease appearance with age and more specifically with low testosterone production [20]. In the studied population of [21], it has been shown that 22% of male over 50 years old has had a T-score equal to or under −2.5 in femoral neck, indicating that elderly men are more susceptible to develop osteoporotic fractures. However, men are less affected by osteoporosis compared to women. As reported by [22], only 6% of the male population over 50 years have a T-score under −2.5 in femoral neck. For men as well as women, testosterone plays an important role in maintaining a healthy bone. It contributes to stimulating bone-forming cell functioning and estrogen production, which, as aforementioned, contribute to bone formation and inhibit bone resorption. Based on this fact, we can conclude that steroid hormone dysregulation is the most influencing factor on bone health, whether for women or men, especially estrogen that induces serious bone degradation for women during menopause.

3.3 Osteoporosis in children

In addition to adults, the risk of developing osteoporosis or having bone fractures is also important in younger patients.

For girls between 11 and 13 years old and boys between 13 and 15 years old, the occurrence of fractures is totally normal. Indeed, bone grows rapidly before the attainment of the peak bone mineral density; thus, during puberty, bone is under-mineralized, which explains the occurrence of fractures in this period independent of developing any bone disease [23, 24]. However, repeated fractures in early age could be one of the causes inducing osteoporosis and the occurrence of frequent fractures in future. In addition to osteoporosis in children, the decrease of BMD can be related to the appearance of some chronic diseases suchlike cerebral palsy and celiac disease [25] or undergoing treatments such as chemotherapy used for children with lympho-blastic leukemia cancer [26, 27].

As shown before, in women's case, estrogen level is one of the biggest promoters of the bone formation phase in the remodeling process. Estrogen level increases due to its secretion by ovaries during the puberty phase for girls, while it circulates in low concentration for boys and girls before their sexual maturity. Thus, the augmentation of estrogen induces longitudinal bone growth during the puberty period [28]. However, a disturbance of estrogen levels could cause critical bone problems as shown by [29], who found that decreasing concentration of estrogen for girls could induce a sideways curvature of the spine known as scoliosis disease.

4. Disease- and treatment-associated bone deterioration

There are several diseases and treatments that destabilize the bone remodeling process and induce abnormal bone deterioration (**Figure 1**) [30]. Each disease and treatment act differently on hormones, which conducts various bone problems. In this

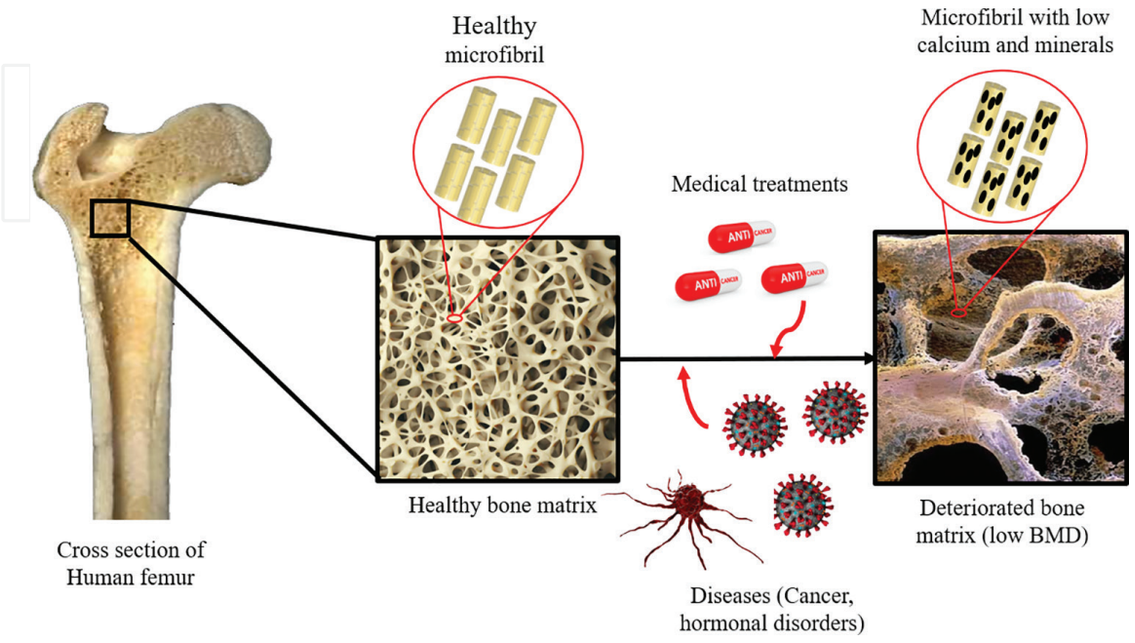

Figure 1.
Illustration of diseases and medical treatments' effect on BMD, bone matrix, and architecture.

section, we are summarizing the most-known diseases and treatments affecting bone and their effect on BMD.

4.1 Disease-associated bone deterioration

Paget disease of bone (PDB): It is a chronic bone disease, considered as the second-most common bone disease after osteoporosis. It is defined as a skeletal growth disorder, leading to bone pain, deformities, deafness, and fractures usually found in the pelvis, spine, femur, and skull [31]. PDB is most common among men than women, and by 50 years of age, the preponderance of being affected by the disease reaches 1 to 5% [32]. The real cause of PDB appearance is not well known. However, many researchers have found a causal relationship between PDB and mutation of the gene encoding sequestosome 1 SQSTM1/p62 that plays an important role in bone-resorbing cell differentiation, activity, and survival [31]. Given this disruption of bone-resorbing cell functioning, the whole bone remodeling process is perturbed, leading to fragile bones and disorganized bone architecture. Otherwise, this disruption causes increased BMD in areas affected by PDB, whether in cortical or trabecular compartments [33].

Osteogenesis imperfecta (OI): Also known as brittle bone disease, OI is a group of rare bone diseases characterized by heterogeneous disturbance of the cognitive tissue. All these diseases are associated with bone mass diminution, increased bone fragility, bone disfigurement, and bone formation insufficiency [34]. OI etiology differs from one disease to another as it depends mainly on the onsets and intensity of each one. Genetic, phenotypic, and functional classifications have been adopted to find out the new causative mutation of OI onset [35]. The most-known OI diseases are X-linked hyposphantaemia, characterized by a mutation of phosphate-regulating endopeptidase that affects vitamin D concentration in the body and consequently bone quality; hypoparathyroidism, characterized by low levels of parathyroid hormone (PTH) that regulates calcium homeostasis; and hypophosphatasia, resulting from the mutation of a responsible gene encoding alkaline phosphatase. The dysregulation of the enzyme disrupts its function to prompt adequate mineralization at an appropriate time in bone tissue. In terms of BMD, OI has been found to be associated with low BMD and also with high BMD in patients with a pathogenic variant of COL1A2, as recently proved by [36].

Myeloma disease (MM): It is a clonal plasma cell proliferative disorder that affects bones by causing bone pain, fractures, and hypercalcemia. It is ranked as the second most-frequent hematological malignancy, with a percentage of 10% [37, 38] in elderly population. This blood cancer is characterized by renal impairment (creatinine >2 mg/dL), hypercalcemia (calcium >11 mg/dL), anemia (hemoglobin <10 mg/dL), the infiltration of clonal plasma with ≥ 60% of the bone marrow, and end organ damage such as lytic lesions in the bone [39, 40]. Because of MM cancer, bone-resorbing cell differentiation is stimulated, and bone-forming cell functioning is suppressed [31]. Due to calcium levels perturbation in blood and bone in addition to bone marrow infiltration, the BMD value is affected.

Breast cancer (BC): It consists of a group of biologically and molecularly heterogeneous diseases that originate from the breast and manifests particularly in the mammary glands. It is the most common type of cancer affecting women worldwide [41]. Whether in its primary state or after metastasizing into the bone, BC affects bones. In a recent research study [42], authors have mimicked bone adaptation during the breast cancer premetastatic state by analyzing the effect of the tumor conditioned

media (TCM) of the breast cancer cell line MDA-MB-231 on mice bone. Based on their experiments, they found that TCM injection into mice induced an increase of bone formation characterized by increased bone mineral apposition and altered bone quality such as high mineralization rate, less bone matrix with more carbonate substitution, and disoriented deposition of minerals. Those findings could explain the results of [43] that found a higher BMD in women newly diagnosed with breast cancer. Otherwise, metastatic BC causes osteolytic lesions due to their stimulation of bone-resorbing cell functioning and repression of the forming cell functioning. The tumor cell and bone cell interactions cause a decrease in bone mass, which leads to less bone mineral density in the matrix [44].

Prostate cancer (PC): This disease consists of a cancer that starts in the gland cells of the prostate. The prostate is a small glandular organ where the seminal fluid is produced. PC has a tendency to spread in surrounding organs such as rectum and seminal vesicles and also to distant organs such as bones through lymphatic and hematogenous routes [45]. Its characterization is tightly related to androgenic hormone signaling such as testosterone [46]. As well as estrogen, testosterone plays an important role in bone remodeling regulation. By its exposure in men with PC, it acts on the bone remodeling process directly or indirectly via aromatization to estradiol, leading to enhanced bone formation and repressed resorption [47]. Probably, because of testosterone increased action, PC patients frequently develop osteoblastic lesions [48]. However, PC is still a risk factor for osteoporosis development, leading to decrease BMD value as shown in the retrospective study of Kwon et al. [49].

Lung cancer (LC): This cancer refers to tumors originating in the lung, which is a spongy organ located in the chest. It is caused due to genetic mutations and disruption in protein synthesis resulting generally from individual cigarette smoking. Those DNA mutations disrupt cells' cycle and promote carcinogenesis [50]. In addition to lung complications, patients with this type of carcinoma develop skeletal complications and fractures. In the work of [51] studying the effect of lung cancer cells on bone cells in mice, authors have found that lung tumor cells secrete inhibitory factors that act on bone-reforming cells and inhibit their mineralization, which induce bone loss and decreased BMD.

Cushing disease: It is an endocrine disorder characterized by a hypersecretion of the adrenocorticotropic hormone (ACTH) by the anterior pituitary, leading to an excessive production of cortisol by the adrenal glands [52]. As well as the abovementioned diseases, Cushing disease is linked with bone degradation. Different factors contribute to bone loss and decreased BMD in patients with Cushing syndrome, including a direct effect of the high secreted glucocorticoids on bone cells, enhanced bone resorption, impaired bone formation, and limited calcium absorption [53].

Hypogonadism: It refers to a failure in the gonads' functioning activity. The gonads are testes for men and ovaries for women; both are the principle organs producing sexual hormones such like testosterone, estrogen, and progesterone and gametes, notably eggs and sperm [54]. This disease could arise from Klinefelter syndrome, Kallman syndrome, pituitary disorders, cancer treatment, obesity, aging, and stress [55]. Given that hypogonadism is related to a failure in sexual hormone synthesis, it is also associated with reduction of BMD, especially if sex steroid deficiency occurs at a young age [56]. For males, for example, a low testosterone level is the main cause of low BMD and increased bone fracture risk for patients with primary and secondary hypogonadism [57].

Hyperparathyroidism: It refers to an endocrine disorder characterized by an abnormal elevation of PTH production by parathyroid glands. This causes hypercalcemia by inducing a loss of calcium from the bones and an excessive gain of calcium in the blood. For that reason, hyperparathyroidism induces serious renal and skeletal problems [58]. Due to calcium deficiency in the bone, hyperparathyroidism has been shown to be associated with increased osteoporosis risk and significantly reduced BMD [58].

4.2 Medical treatment-associated bone deterioration

Glucocorticoids: They are a sort of drugs composed of primary stress hormones that regulate various physiological processes [59]. They are used as anti-inflammatory, antiallergic, and immunosuppressive to treat different disease types and more often inflammatory skin disorders such like allergic contact eczema and toxic-irritative eczema [60, 61]. Given its nature, an excess of glucocorticoids leads to reduced calcium intestinal absorption and calcium renal excretion and sex steroid level decrease, which affects bone remodeling by stimulating bone repression and inhibiting formation, leading to bone loss, low BMD, and elevated risk of fracture [62].

Radiotherapy: It consists of using X-rays or subatomic particles directly on tumor cells in curative and palliative settings [63]. Thanks to this procedure, cancer cells shrink, and the local cancer recurrence is reduced [64]. However, RT noticeably affects bone quality, leading to fragility in the zones surrounding the treated tumor area. Indeed, RT decreases cellularity; affects bone-forming cell differentiation, proliferation, and production; and stimulates bone-resorbing cell differentiation using low radiation doses [65]. This explains the significant decrease in BMD value in the area treated with RT as noticed in [66] study investigating RT effect on lumbar vertebrae in women with cervical cancer [66].

Chemotherapy: It involves the use of chemical agents capable of destroying cancer cells by either affecting their macromolecular synthesis by interfering with their DNA or affecting the appropriate functioning of the preformed molecule. This limits cell proliferation and consequently their invasion. Besides their good efficacy on cancer cells, chemotherapy has toxic effects on normal cells, including bone cells, which affects bone quality [67]. Ovarian failure and negative and positive effects on osteoblastogenesis and osteoclastogenesis, respectively, due to chemotherapy induce bone loss [68, 69] in addition to loss of bone mineral density as found in (Bone mineral density change during adjuvant chemotherapy in pediatric osteosarcoma), where children under chemotherapy have shown a decrease of BMD in lumbar spine and femoral neck especially at the end of the therapy [70].

Aromatase Inhibitors (AIs): These are medications used for the treatment of breast cancer, notably estrogen receptor positive, by blocking estrogen synthesis [71]. Because of their action on estrogen, women undergoing AI develop osteoporosis, which induces bone fractures and leads to up to 2.6% loss of BMD per year in lumbar spine [69].

Androgen deprivation therapy (ADT): As well as AIs, ADT is also a treatment controlling sex hormone synthesis, more precisely suppressing or blocking the production or action of male hormones, notably testosterone. Given the important role of testosterone already mentioned, ADT induces osteoporosis. Its effect is much higher than that of AIs as it has been found that ADT causes 4.6% loss of BMD per year in lumbar spine, while AIs induce approximatively 2.6% of BMD decrease [69].

Bone marrow transplant: It is a procedure in which heathy hematopoietic stem cells are administrated into the patient to replace the depleted bone marrow with dysfunctional cells that have been destroyed by treatments such as radiation or high doses of chemotherapy. This permits to supplement bone marrow functioning and to destroy treated malignant tumor cells. The healthy stem cells come from the bone marrow of the patient or from a donor [72]. The hematopoietic cell transplantation has also been identified as one of the medical procedures causing reduced BMD. The major causes of this loss are low sexual hormones notably estrogen and testosterone, secondary hyperparathyroidism due to reduced calcium concentration, and post-transplant steroid therapy—50–60% of patients undergoing this therapy undergo bone loss [73]. In the work of [74], authors have noticed a significant loss in BMD value in the hip, reaching 4.2% for men and women under observation over 1 year of treatment.

5. Medical treatments and dietary recommendation for BMD alteration

The goal of pharmacological therapy is to reduce the risk of fractures by acting on the main agents controlling bone remodeling, which has been affected by osteoporosis. The majority of osteoporosis treatment is antiresorptive (e.g., denosumab, bisphosphonates, estrogen agonist and antagonist, estrogens, and calcitonin), which reduces bone resorption. Otherwise, some anabolic treatments have been developed (e.g., teriparatide), which are dedicated for stimulating bone formation instead of repressing bone-resorbing cell functioning [75]. Both antiresorptive and anabolic agents improve BMD but with variated intensities and can be used for the treatment of one patient. In the work of [76], authors found that the treatment sequence played an important role in osteoporosis treatment. Based on their observation, they have concluded that initiating a treatment by anabolic treatment first followed by a potent antiresorptive treatment is more effective in improving BMD value. In contrary, using antiresorptive agents first, then when the BMD does not sufficiently increase, clinicals suggest to switch to teriparatide, which is not optimal utilization of anabolic treatments.

Besides medications, dietary habits contribute also to improve or deteriorate the bone. Vitamin D and calcium form part of the bone mineral matrix, assuring its strength, and one of the best ways to reach adequate intake of calcium and vitamin D is through healthy eating habits [77]. In a recent meta-analysis of the influence of foods rich in vitamin D on serum 25(OH)D levels, results have shown that those aliments lead to significant increase in serum 25(OH)D as well as BMD [78]. Together with vitamin D, increased calcium intake has been proven to improve BMD by 0.6–1% over 1 year [79]. However, in a recent study [80], dietary calcium intake has not show any association with BMD values in normal participants over 50 years of age, while it has shown a positive change in BMD in women undergoing osteoporosis medical treatment.

6. Conclusion

To maintain its multiple functions, bone is renewed periodically, assuring resorption of old bones and formation of new matrix. However, naturally with age, the process of bone renewing is altered with higher bone resorption and decreased matrix

deposition, which lead to decreased BMD and increased fracture occurrence. Several diseases and treatments contribute to or engender osteoporosis or other bone problems. Those diseases and treatments generally affect hormones or bone mineral levels. The most important hormones for a normal bone remodeling process are: (i) estrogen, (ii) testosterone, and (iii) cortisol. And the most important mineral disturbed is calcium. When the absorption of calcium by the bones is inhibited, bones deteriorate easily and undergo fractures. In order to limit the side effects of treatments and additional bad impacts of diseases, using anabolic and antiresorptive treatment is mandatory accompanied by good dietary habits.

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Conflict of interest

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