Chapter

Mechanobiological Behavior of a Pathological Bone

Imane Ait Oumghar, Abdelwahed Barkaoui and Patrick Chabrand

Abstract

Bone density and bone microarchitecture are two principle parameters needed for the evaluation of mechanical bone performance and consequently the detection of bone diseases. The mechanobiological behavior of the skeletal tissue has been described through several mathematical models. Generally, these models finger-board different length scale processes, such as the mechanical, the biological, and the chemical ones. By means of the mechanical stimulus and the biological factors involved in tissue regeneration, bone cells' behavior and bone volume changes are determined. The emergence of bone diseases leads to disrupt the bone remodeling process and thus, induces bone mechanical properties' alteration. In the present chapter, an overview of bone diseases and their relationship with bone density alteration will be presented. Besides, several studies treating bone diseases' effect on bone remodeling will be discussed. Finally, the mechanobiological models proposed to treat bone healing and drugs' effect on bone, are going to be reviewed. For this sake, the chapter is subdivided into three main sequences: (i) Bone remodeling, (ii) Bone deterioration causes, (iii) Mathematical models of a pathological bone, and (iv) Mechanobiological models treating bone healing and drugs effect.

Keywords: mechanobiological modeling, bone remodeling, mathematical models, bone diseases, bone healing, drugs

1. Introduction

An adult body skeleton is renewed once each 10 years as a median frequency. The renewing is the result of a biological process, persisting in the human body, known as bone remodeling. This biological phenomenon has been defined, for the first time, as a dynamic process [1]. It permits to maintain the mechanical bone strength by preserving the most important minerals' homeostasis. It consists of a spatial and temporal coupling of two main phases: (i) old bone resorption and (ii) new bone formation. This process is controlled by a variety of signaling mechanisms that orchestrate bone cells functioning. These cells are: (i) osteoblasts, (ii) osteoclasts, and (iii) osteocytes. Osteoblasts are mononucleated cells that derive from mesenchymal stem cells (MSCs), which originate in the bone marrow. These lasts are responsible of bone formation. Then, osteoclasts are multinucleated cells that derive from hematopoietic stem cells, which are notably produced in the bone marrow. These lasts are the only cells able to degrade bone [2, 3]. Eventually, osteocytes are the cells type that represent the highest amount of bone cells in the

body (90–95%) [4]. They are the result of the last differentiation of the osteogenic lineage and have a mechanosensing feature that allow them to feel the mechanical loading applied on the bone matrix and release various signaling factors that triggers the other bone cells to start their activity. During bone remodeling process, these cells are interacting with each other and various biochemical and mechanical factors are orchestrating their functioning [5]. Bone diseases emerge when the normal process of bone remodeling is interrupted. This result is generally occurring when the balance of the biochemical factors controlling the process is lost. Indeed, there are many types of bone diseases. Yet, some of them are more common than the others. The most prevalent types of bone problems are osteoporosis, Paget's disease of bone, and cancer-associated bone loss. Three cancer types are affecting a large slice of society and induce bone degradation and fracturs: Multiple myeloma, Breast cancer, and Prostate cancer. Several studies have been interested in analyzing these bone diseases' effect and also drugs' effect on bone remodeling process [5–8] to predict the bone behavior after getting affected by the disease and determine to which extent a treatment's type or specific dose are reducing the effect of the disease. In the present chapter we are going to provide a description of bone remodeling and some diseases feature, then to present the different mechanobiological models dealing with bone diseases and drugs' effect on bone remodeling. The chapter is subdivided into three main sequences: (ii) Bone deterioration causes, (ii) Mathematical models of a pathological bone, and (iii) Mechanobiological models treating bone healing and drugs effect.

2. Bone remodeling

2.1 Generalities

The cell activity leading to bone renewing has been identified by Frost [9] as a bone multicellular unit (BMU). A mature BMU contains a group of osteoclast and osteoblast cells, in addition to blood supply associated with the connective tissue. Knowing that the lifespan of a BMU is higher than the cells one, new osteoclasts and osteoblasts have to continually adhere to the BMU space in order to maintain its operation [10]. The bone multicellular units are presented in our skeletal under the form of discrete foci that could take different shapes, such as the unidirectional, the branched, and the clustered forms [11]. These foci move forward in all bone compartment to assure the renewing of concerned places with a longitudinal advance rate of 25 μm/day [12].

In order to characterize and discover precisely the movement of bone cells during the remodeling process, researchers have identified four phases of this biological phenomenon. First, the activation phase where osteoblasts are excited to release resorbing cytokines, after receiving the biological signal transmitted by osteocytes. Osteocytes are a bone cells that are embedded in the bone matrix and have the ability to sense the mechanical force applied upon the bone. Resorbing cytokines are responsible of the osteoclasts' recruitment. The involvement of these cells engenders the start of resorption phase. During this remodeling step, active osteoclasts erode the damaged bone matrix by means of ions, acid, and enzymes [13, 14]. Thereafter, macrophages appear into the gap created and clean the surface from the remaining bone debris. This step is called the reversal phase and it is essential to prepare a clean surface for matrix formation. In order to fill in the bone lacunae, active osteoblasts migrate into the concerned surface and produce the osteoid, which gets gradually mineralized [15]. The final result of bone remodeling is, thus, a new, healthy, and stronger bone matrix.

2.2 Bone cells regulation

As shown above, osteoblast, osteoclast, and osteocytes are predominantly controlling the bone turnover. Thus, it is essential to understand the different steps of these cells differentiation and how biological factors are regulating their activity.

2.2.1 Regulation of osteoblasts

Osteoblasts are mononucleated cells that derive from mesenchymal stem cells (MSCs), which originate in the bone marrow. Those cells are multipotent stromal cells that have the ability to differentiate into a multitude of different cells thanks to their gene expression program. Among these cells, we can find osteoblasts, fibroblasts, adipocytes, and chondrocytes [16, 17]. The first step of osteoblastogenesis is regulated by Wingless-int (Wnt), specifically the Wnt10b protein coding gene. In [18], the authors proved that Wnt plays a key role in the stimulation of MSCs differentiation into osteo/chondro progenitors and the inhibition of preadipocyte commitment. Several other biological factors are involved in MSC differentiation into active osteoblast. Among which we can cite Runt-related transcriptor factor (Runx2), Osterix (Osc), Alkaline Phosphatase (ALP), type 1 parathyroid receptor (PTH1R), Osteopontin, and sialoprotein 2 (BSP II) (**Figure 1**). The process is described in details in [19].

Based on these information, we can deduct that osteoblastogenesis is a couple of complex biological interactions involving various factors where a simple alteration could destroy the whole system. For instance, Runx2, plays an important role in skeletal development. However, high amount of this transcription factor could inhibit the osteoblast maturation process and lead consequently to osteopenia disease [20]. Concurrently, other factors such as bone morphogenetic proteins (BMPs), transforming growth factor beta (TGFβ), parathyroid hormone (PTH), and fibroblast growth factor (FGF) have been judged as critical regulator factors of Runx2 [21]. Aside from Runx2, Wnt/β-catenin and BMPs have also a huge impact on bone formation and precisely on osteoblastogenesis regulation [22–24].

2.2.2 Regulation of osteoclasts

Osteoclasts are the only cells able to degrade the bone [2, 3]. They derive from hematopoietic stem cells, which are produced in the bone marrow. By dint of the macrophage colony stimulating factor (M-CSF), these stem cells are differentiated into macrophages and osteoclast progenitors. M-CSF is known as one of the main stimulator factors of osteoclastogenesis as it stimulates preosteoclasts proliferation and their expression of receptor activator of NFkB (RANK), that represents a key

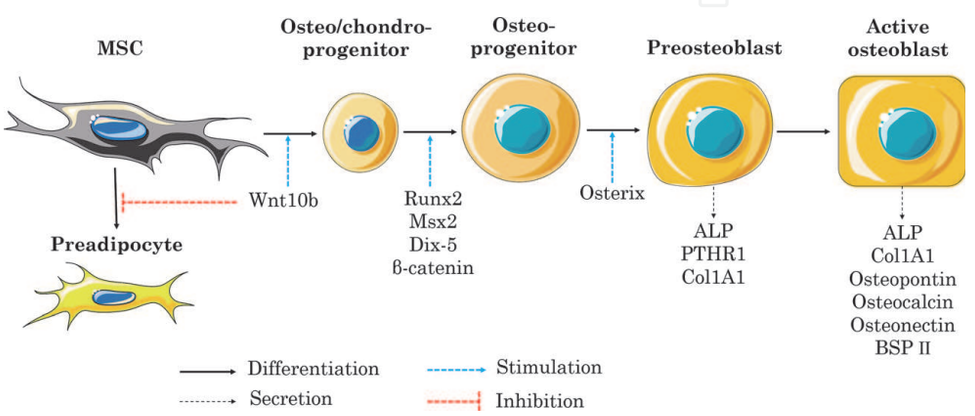

Figure 1.
Schematic representation of oteoblastogenesis process.

factor in osteoclasts maturation. Indeed, additionally to its principal function of bone synthesize, osteoblasts have been reported to regulate osteoclastogenesis through its secretion of the M-CSF and the receptor activator of NFkB Ligand (RANKL). According to the literature, RANKL is also secreted by osteocytes [25]. This ligand expression is stimulated by various types of hormones and factors such as PTH, prostaglandin E2 (PGE2) and 1.25-dihydroxyvitamin D3 ($1.25(OH)_2D_3$). Indeed, RANKL's interaction with its receptor RANK is mandatory for osteoclasts' differentiation, maturation and activation as it induces the recruitment of many hormones inside the preosteoclasts. RANK/RANKL binding simulates the recruitment of the tumor necrosis factor receptor associated factor 6 (TRAF6), which triggers a succession of interactions leading to osteoclastogenesis transcription. During osteoclastogenesis the osteoclast progenitors get differentiated into preosteoclasts. Then as a result of preosteoclasts fusion, mature multinucleated osteoclasts are created, where the nuclei's number can variate between four to twenty nuclei [26].

2.2.3 Regulation of osteocytes

Osteocytes represent the highest amount of bone cells in the body (90–95%) [4]. They are the result of the last differentiation of the osteogenic lineage. Indeed, during bone gap filling, some osteoblasts get trapped into the osteoid and differentiate into osteocytes [27]. Some authors have distinguished between several stages of osteocytogenesis. Based on [28], it has been mentioned that the transition from osteoblasts into osteocytes is governed by seven stages: (i) osteoblast, (iii) osteoblastic osteocyte (Type 1 preosteocyte), (vi) osteoid osteocyte (Type 2 preosteocyte), (v) Type 3 preosteocyte, (vi) young osteocyte, and (vii) old osteocyte. Throughout the transition, a multitude of actions took place. Actually, during all these differential stages, the cell undergoes many morphological changes to become a cell with dendritic extensions [29, 30]. In contrary to MSC to osteoblast transition, the signaling mechanisms during the process governing osteoblast to osteocyte transition is poorly understood. However, some authors have recently found some regulating factors impacting the process such as PTH and insulin-like growth factor type 1 (IGF-1) as, according to [31], they enhance osteoblast-osteocyte differentiation. The osteocytes surround the blood vessels in a cylindrical way and are organized in parallel to the bone surface. They are interconnected between each other by means of their dendritic extensions that occupy tiny canals called canaliculi. These canaliculi permit the transduction of biochemical signals to other osteocytes and bone cells located in the surface [32, 33]. Thanks to their characteristics, osteocytes are the best known for their ability to sense the mechanical loadings and transmit the information to the other bone cells in such a way the bone remodeling process can start.

2.3 Bone remodeling cycle

Bone remodeling process (**Figure 2**) as mentioned before is a succession of events governed by many biochemical factors. In this section, the most important interactions, actions and reactions are described in summary to show the bone cells dynamics and their effect on the bone mass changes.

2.3.1 Activation

1. Mechanical loading applied on the skeletal

2. Osteocytes are excited

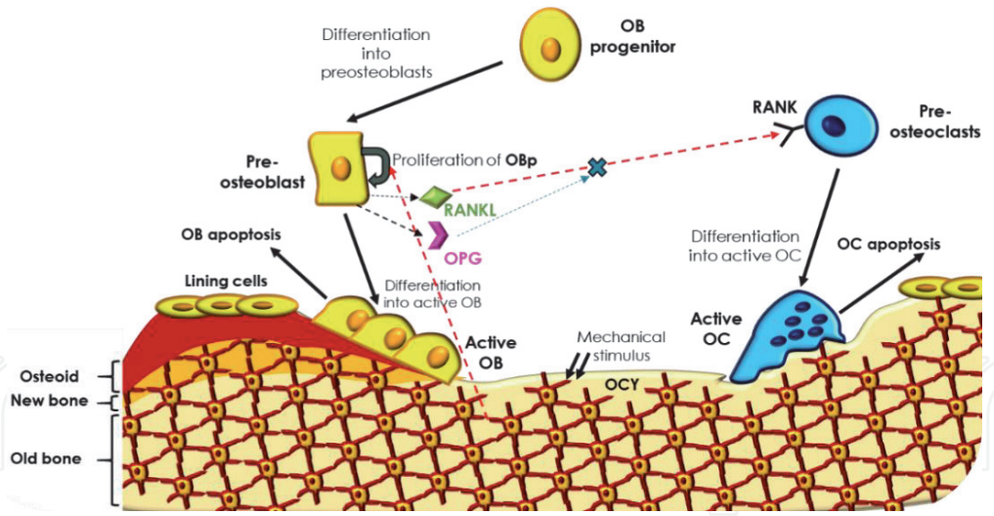

Figure 2.
Schematic representation of bone cells main biochemical interactions during bone remodeling process.

3. Osteocytes release biochemical factors stimulating osteoblasts and osteoclasts (e.g. nitric oxide (NO), sclerostin (SCLR), M-CSF and RANKL) promoting osteoblast proliferation and osteoclasts differentiation.

4. MSCs release biochemical factor stimulating osteoclastogenesis (e.g. M-CSF and RANKL)

2.3.2 Formation

1. Differentiation, proliferation, and activity of osteoclasts. The osteoclastogenesis is mediated by RANK-RANKL binding.

2. Active osteoclasts secrete hydrogen ions and acid phosphatases

3. Mineral phase of the bone matrix is dissolved

4. Active osteoclasts secrete enzymes

5. Organic phase of the bone is resorbed, and embedded biochemical factors are released (e.g. TGFβ and BMP)

6. Osteoblastogenesis is stimulated and osteoprotegerin (OPG) amount increases inducing RANKL decrease

7. Osteoclasts undergo apoptosis

2.3.3 Reversal

1. Macrophages clean the bone lacunae from bone matrix debris

2. Active osteoblasts adhere to bone lacunae

2.3.4 Formation

1. Active osteoblasts synthetize the collagen to produce the osteoid that gets gradually mineralized.

2. At the end osteoblasts differentiate into osteocyte, lining cells or undergo apoptosis

2.3.5 Termination

1. Signals exciting bone cells decreases in the area

2. BMU recruitment gets smaller

Any interruption of the biological pathways, during remodeling process, can lead to enormous consequences on the bone cells functioning, which in its turn leads to very dangerous diseases.

2.4 Bone mechanobiology

The mechanobiology particularity of bone tissue is the base source of its renewing ability and its capacity to be adapted to external charges. Based on many experimentations, researchers have found noticeable changes in bone mass, while variating the external applied charges on the skeleton [34–39]. Thanks to the bone microarchitecture and its tissue composition, the mechanical loads are transmitted at the cells' level as a combination of fluid shear stress and extracellular strain matrix [40]. Then, thanks to the osteocytes' mechanosensing mechanisms like ion channels, integrins, gap junction, and actin cytoskeleton, these cells become able to release biochemical components (e.g. proteins and cytokines) that regulates osteoblasts and osteoclasts' activity (e.g. increasing their proliferation/differentiation and inhibiting their apoptosis). For the sake of illustration, we mention the most known biochemical factors involved: PGE2 [41], NO [42], and SCLR [43]. In addition to osteocytes, osteoblasts have also been classified as a mechanosensory cell as their respond to the mechanical signal mediated by the fluid flow by upregulating the cyclooxygenase-2 (Cox-2) and c-fos and producing intracellular calcium (Ca^{2+}).

3. Bone deterioration causes

3.1 Normal bone diseases

3.1.1 Osteoporosis

Osteoporotic bone is a fragile bone characterized by a low mass (**Figure 3**) and deteriorated microstructure. These features are making this bone highly susceptible to fractures. Osteoporosis is a biochemical problem resulted from both osteoblast and osteoclast behaviors' dysregulation that leads to excessive bone resorption. It affects a large slice of the world's population, especially women, and it causes physical debilitation and frequent fracture incidence in patients. Osteoporotic fractures are generally occurring in the spine, hips, femur, and forearm; and they can be detected in case of a drop in the bone mineral density (BMD) value in the fractured area [44]. Based on the disease type, scientists have subdivided osteoporosis into two categories: (i) the primary osteoporosis, which is related to age and hormonal dysregulation, or unknown causes. This latter case is called idiopathic primary osteoporosis [45]. Then, (ii) the secondary osteoporosis, which is related to other diseases appearance (e.g. cancer, hematologic, and gastrointestinal diseases), or to some treatments use (e.g. Cancer chemotherapeutic drugs, glucocorticoids, and anticonvulsants [45]).

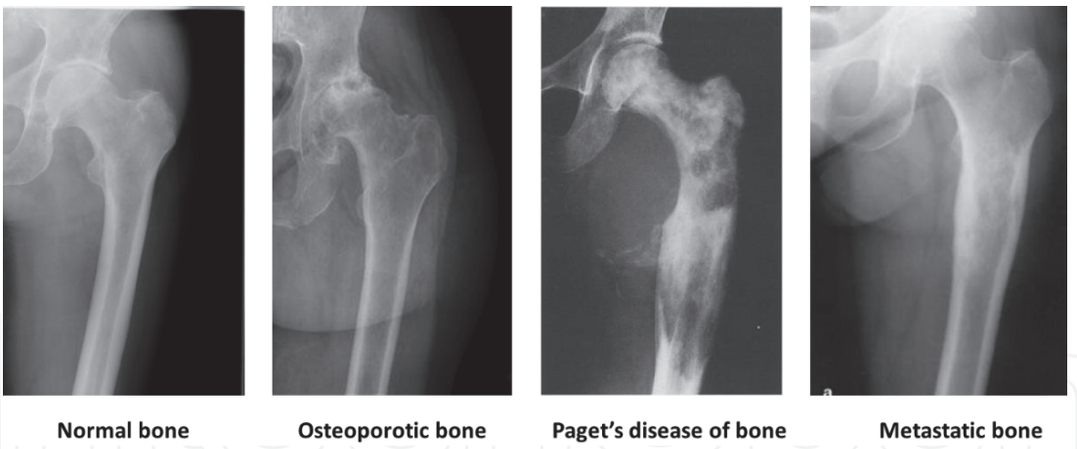

Figure 3.
Difference between normal proximal femur and femur affected by osteoporosis, Paget's disease, and cancer, based on medical images.

3.1.2 Paget's disease of bone

Paget's disease of bone is a chronic bone disease, that affect either a single or multiples parts of the skeletal. The concerned areas are characterized by increased bone resorption accompanied with increased but disorganized bone formation [46] (**Figure 3**). These problems in the bone remodeling process causes deformed and weak bones. Generally, this disease affect men and the elderly more than women and young people [47]. The real etiology of this disease is still unknown, however, 40% of patient affected by Paget's disease have been detected to have a family history of SQSTM1 gene mutation with a protein regulating osteoclasts called p62 [48]. Advanced Paget's disease of bone could cause several complication to the patient, among which, bone pain, bone fractures, and hypercalcemia [49].

3.1.3 Osteogenesis imperfecta

Also known as brittle bone disease, osteogenesis imperfecta 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 [50]. Osteogenesis imperfecta etiology-associated differ from a disease to another as it depends mainly on the onsets and intensity of each one. Genetic, phenotypic and functional classification have been adopted to find out the new causative mutation of osteogenesis imperfecta onset [51]. The most commonly known osteogenesis imperfecta diseases are: (i) X-linked hyposphantaemia (XLH), which is characterized by a mutation of phosphate regulating endopeptidase (PHEX) leading to dysregulate 1,25 OH vitamin D levels; (ii) Hypoparathyroidism, which is characterized by PTH deficit that regulate calcium homeostasis; (iii) Hypophosphatasia, which results from mutation of a responsible gene of encoding ALP called ALPL. The dysregulation of the enzyme disrupts its function to prompt adequate mineralization at an appropriate time in bone tissue; and (vi) Osteopetrosis caused by gene mutation code for RANK and RANKL, leading to an impairment of osteoclasts and thus increased bone mass with a deterioration of bone quality resulting in atraumatic fractures.

3.2 Metastatic bone diseases

Bone degradation is related to several different factors among which, cancer is the most discussed issue. Regardless of the cancer type, cancer patients have a

higher risk of bone loss than the rest of the population [52]. In fact, bone microenvironment enables tumor cells to home, proliferate, and colonize [5]. Thus, generally, cancer cells migrate form their inherent location to bone microenvironment, were osteoblasts and osteoclasts secrete important biochemical factors for their survival [53]. Each cancer type secretes special biochemical factors affecting bone environment and stimulating their growth. The spread of tumor causes the so-called bone metastasis disease either if it is a solid tumor (e.g. prostate cancer, breast cancer) or a liquid tumor (e.g. multiple myeloma). Bone metastasis incidence is mostly occurring in multiple myeloma patients (95–70%), breast cancer patients (75–65%), and prostate cancer patients (75–65%) [54].

3.2.1 Multiple myeloma

Multiple myeloma is a blood cancer disease characterized by an abnormal growth of B-lymphocytes, while differentiating into plasma cells. This 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, and end organ damage such as lytic lesions in the bone [55, 56]. As mentioned before, this disease is tightly related to bone degradation. Located in the bone marrow, multiple myeloma cells are able to interact with bone remodeling cells by means of adhesion molecules to proliferate and survive [57]. Indeed, multiple myeloma adhesion incite osteoblastic cells to release interleukin- 6 (IL-6), which has an essential role in tumor growth and survival [5, 58]. Studies found that multiple myeloma growth affect both bone formation and bone resorption. On one hand, they stimulate the differentiation and activity of osteoclasts by secreting RANKL, the interleukins IL-1, IL-3, IL-6, and the parathyroid hormone-related protein (PTHrP) that in turn stimulate RANKL expression by osteoblasts. Additionally, they express syndecan-1, which is a type 1 transmembrane proteoglycan, that binds OPG [59]. This multiple effects on RANK/RANKL/OPG pathway enhances osteoclastogenesis and consequently bone resorption. On the other hand, multiple myeloma cells inhibit the osteoblastogenesis by expressing some biochemical factors such like Wnt and dickkopf-related protein 1 (DKK-1) [60].

3.2.2 Breast cancer

Breast cancer is a common disease among postmenopausal women. It is characterized by an abnormal growth of breast epithelial cells. Multiple factors are related to this disease incidence including age, as advancing age increases the risk of getting breast cancer, gender, as women are the most concerned, personal or family history of breast cancer, and exogenous hormone use, as some treatments increasing sex hormones notably estrogen and progesterone [61]. Brest cancer develops because of DNA damage that could be the result of sex hormones exposure [62]. Epithelial tumor cells tend as well as the other cancer types, to migrate into the bone microenvironment and interact with bone cells. Actually, breast cancer tumor cells stimulate RANKL expression and inhibit the OPG one by expressing a multitude of biochemical factors, among which we note the interukins IL-1, IL-6, IL-8, IL-11, M-CSF, BMP, DKK-1, PGE2, PTHrP [63]. As a consequence, tumor prevalence in the bone area induces bone loss.

3.2.3 Prostate cancer

Prostate cancer is a common disease among elderly men, which usually leads to death as it is the case in the USA [64]. It is characterized by an abnormal growth of

the prostate basal and luminal epithelial cells [65]. The real etiology of prostate cancer is still unknown, however, there is some factors related to its incidence. For instance, age, as advancing age increases the risk of getting prostate cancer, family history of prostate cancer, and using dietary supplement rich of vitamin E [66]. Similarly to multiple myeloma and breast cancer, prostate tumor cells also adhere to bone microenvironment and interact with bone cells. It has been reported that prostate tumor cells secrete PTHrP, Wnt and DKK-1 that regulates osteoblast and osteoclast behavior once settled in the bone [67, 68]. Thereafter, when prostate cancer cells adapt to the new environment, they start secreting the prostate- specific antigen (PSA), that inhibit PTHrP. The high amount of Wnt stimulate osteoblasts differentiation, and thus RANKL amount increase. When RANKL increases, bone resorptions is enhanced as result, and the biochemical factors incorporated in the old bone are released stimulating tumor cells proliferation [7].

4. Mathematical models of a pathological bone

Several studies have been interested in bone diseases' effect on bone remodeling process [5]. A large number of the mathematical models, developed in this regard have been concentrated on the biological aspect related to bone remodeling, so that they can provide a better understanding of the disease biological effect on the process.

4.1 Normal bone diseases

Osteoporosis, as it is the most widespread bone disease and the most known bone problem, it has captured the attention of many authors, especially those developing bone remodeling mathematical models. Through their mathematical models, the authors try to schematize as best as possible the osteoporosis disease in such a way the results could fit the experimental data.

In their study [69], Lemaire and co-authors have investigated the effect of osteoporosis on the normal biochemical interactions during remodeling process. They opted for the implementation of three osteoporosis causes: (i) estrogen deficiency, (ii) vitamin D hormone calcitriol ($1.25(OH)_2D_3$) deficiency, and (iii) glucocorticoid excess. These osteoporosis' causes have been implemented by changing some parameters' value in the principal bone remodeling mathematical model. According to authors, estrogen deficiency could be represented by decreasing OPG's production rate parameter until osteoclast to osteoblast concentration ratio reaches 5 in the steady state. Then, concerning vitamin D deficiency, it could be represented by increasing the PTH production rate, while glucocorticoid excess could be schematized by decreasing osteoblast progenitors' differentiation rate. The choices made by the authors are inspired from the literature: (i) authors have choose to decrease PTH production, as originally estrogen expression is stimulating OPG production [70], (ii) PTH effect on bone cells changes with vitamin D3 deficiency, thus PTH production rate alteration has been based on experimental observations [71], and (iii) Glucocorticoid induces a decrease in the core binding factor A1 (Cbfa) that is important for osteoblast differentiation, thus, the rate of preosteoblast differentiation has been reduced to mimic the glucocorticoid excess effect osteoblastogenesis [72].

Targeting the same objective, Pivonka et al. [73] have studied the RANK-RANKL-OPG signaling pathway to model osteoporosis disease in postmenopausal women. In their research study, the catabolic bone disease has been represented

firstly by decreasing the OPG production value, then by testing a combination of changed parameter related to the components RANK-RANKL-OPG. The combination used in the model is based on [74]'s work, where RANK responsiveness and RANKL production are up-regulated, while OPG production is down-regulated. These changes enhanced osteoclasts' response comparably to the osteoblasts' one. However, the intensity of bone resorption resulted is different from changing one parameter to three parameters. Indeed, it has been observed that a change in one single parameter leads to less sever bone resorption. Overall, the obtained numerical results were qualitatively consistent with the experimental observation related to RANK/RANKL/OPG system changes in the case of postmenopausal osteoporosis (PMO) bone disorder.

Apart from osteoporosis, Paget's disease has also interested some researchers, but another time the model developed considering this bone problem have only treated the biological side of the remodeling process. The work of Komarova et al. [75] have illustrated the bone cells dynamics in the presence of Paget's disease. To proceed, authors have altered the parameters representing the normalized activity of resorption and formation parameters in addition to the autocrine parameters. Their model has demonstrated more sensitivity to changes made on the autocrine parameters' values. These changes lead to increase bone resorption succeeded by increased bone formation and represented nearly the same effect of Paget's disease of bone. Nevertheless, the real biological process or the particular effects inducing this type of bone diseases have not been deemed.

4.2 Metastatic bone diseases

Being one of bone metastasis causes, cancer seems to be an important subject to treat for the clinical interest. As shown before, different types of cancer are causing bone loss, that could be sometimes escorted by bone formation. These bone changes are due to the cancer cells growing inside the bone, that represents a rich area assuring their expansion.

The paper of [76] have treated the problem of cancer's effect on bone health independently of the cancer type. Based on a mathematical model composed of differential equations, authors have calculated bone cells number's variation, which depend either from a normal biological process or a disrupted process controlled by tumor cells growth. According to the tumor growth, the type of bone disorder (i.e. osteolysis or osteosclerosis) is deducted. Therefore, the types of biochemical released factors controlling the process are identified (i.e. TGFβ and PTHrP for osteolysis case/TGFβ and IGF for osteosclerosis case).

In more detailed studies, authors have opted for specific cancer's type effect on the remodeling process. For instance, a mathematical model have been described by Farhat et al. [7] to quantifying bone remodeling changes within the existence of prostate tumor cells in the bone microenvironment. Based on a large literature study, the authors managed to detect the main biological factor controlling the interactions between bone cells and the tumor's one. In summary, authors have made the following assumptions:

- Uncommitted osteoblast differentiation into preosteoblasts is governed by either TGFβ and Wnt.

- Preosteoblasts' differentiation is controlled not only by TGFβ, but also by the Wnt. Wnt is playing an activator role in the process, while TGFβ is inhibiting the differentiation.

- Active osteoclasts apoptosis is variating from a given base rate, then, it follows TGFβ's concentration as it performs as a stimulator factor of active osteoclasts' death.

- Bone formation is controlled by calcium concentration, which plays a stimulating function, rather than being only relied to active osteoblast concentration.

Through this article, prostate cancer growth's impact on the bone remodeling process has been properly established as each influencing factor has been simply explained. According to the results, prostate cancer cells existence induces an increase of RANKL-OPG ratio and bone production. Besides, they found that there are two osteogenic states over the course of disease.

Multiple myeloma's influence on bone remodeling has captured more attention than the other cancers. The research article [6] has provided a model schematizing multiple myeloma cells' growth impact on bone cells dynamics. The model has not clearly shown the biochemical effect of these malignant cells on the normal process. Although, it has shown their effect on the autocrine and paracrine parameters described previously in [75]. Authors have suggested a tumor density differential equation to schematize the metastasis evolution, and they have implemented it mathematically into the paracrine and autocrine variables to disrupt the normal oscillation of bone cells during remodeling cycles. This study findings have completely represented multiple myeloma effect on bone mass evolution. However, the biological interaction occurring between tumor cells and bone cells have not been explicitly shown. Thus, the effect of biochemical factors is not clearly presented.

One year later, a study considered precisely the main biological interactions occurring during a remodeling process affected by multiple myeloma's actions. In the model suggested by Wang et al. [77], multiple myeloma cells behavior have been modeled by differential equations, which permit to calculate the concentration of the principal biochemical factors affecting the bone cells. These factors are the interleukin 6 IL-6, which is secreted by uncommitted osteoblasts promoting multiple myeloma tumor cells' proliferation, and the very-late antigen 4 (VLA-4), which mediate Multiple myeloma-Bone marrow-derived mesenchymal stem cells adhesion and promote IL-6 expression. This antigen effect appears after VLA-4 binding vascular cell adhesion molecule 1 (VCAM-1) expressed by the uncommitted osteoblasts. A further investigation of the problem has been done by [78], where, additionally to the previous biochemical factors incorporated in the model of [77], they have added the effect of small leucine-rich proteoglycan (SLRPs). This regulator is secreted by active osteoblasts. Its main function, in the case on multiple myeloma tumor cells existence, is to inhibit their proliferation. Through this work, the biochemical mechanism controlling the bone remodeling is clearly described and properly established by means of the proposed system of differential equations.

5. Mechanobiological mathematical models of a pathological bone

In contrary to strictly biological mathematical models, bone diseases have been also incorporated into mechanobiological mathematical models, where the mechanical aspect is taken into consideration. Nevertheless, very few bone diseases have been discussed through these models. In this chapter, we are going to present the mechanobiological models treating osteoporosis problem. All the presented models are based on biological bone remodeling models that represent bone cell

population through differential Equations [79]. These equations permit to determine bone cells' concentration variation over time. The behavior of these cells is controlled by the most influencing biochemical factors that exist in bone area within remodeling process.

In the work [80], authors were interested in explaining the experimentally changes of bone mass in postmenopausal women suffering from osteoporosis, without neglecting the mechanical influence on the process. Indeed, bone cells concentration variation over time has been controlled by biochemical factors and also by the mechanical strains in the extravascular cortical bone matrix. An activation function $\Pi_{act,OBa}^{mech}$ (Eq. (1)), representing strains in the extravascular area, was used to promote preosteoblast proliferation and RANKL production. The mechanical stimulus represented by strain energy density (SED) has a minimum and maximum values that correspond respectively to the threshold SED values $\Psi_{bm,min}$ and $\Psi_{bm,max}$. Indeed, according to the literature, RANKL/OPG ratio is affected by hydraulic pressure at the microscopic level [81]. Therefore, RANKL production function has been formulated as a function of the SED sensed at the bone matrix's level. On the other hand, the effect of postmenopausal osteoporosis has been implemented by considering the effect of mechanical feedback on the progress of PMO. First, authors have fixed a production rate of PTH that reflect the PMO and then they variated the maximum proliferation rate of preosteoblasts depending on the mechanical stimulus' level. Based on this, various PMO-scenarios have been established by changing the value of the strength of anabolic strength parameter . This parameter represents the slope of the activation function. Hence, it determines the degree of which the SED should be increased to reach the maximum value of the activation function that allows a maximum proliferation rate to the preostoblasts.

$$\Pi_{act,OBa}^{mech} = \begin{cases} 1/2 & \Psi_{bm} < \Psi_{bm,min} \\ 1/2\left(1+\lambda\left(\dfrac{\Psi_{bm}}{\Psi_{bm,min}}-1\right)\right) & \Psi_{bm,min} < \Psi_{bm} < \Psi_{bm,max} \\ 1 & \Psi_{bm,max} \leq \Psi_{bm} \end{cases} \quad (1)$$

Based on the results, bone porosity, calculated based on the bone remodeling mathematical model, was able to show the severity of PMO evolution over time. According to the authors, the negligence of the mechanical feedback in the presence of PMO disease, lead to unbounded bone resorption, which doesn't reflect the reality. Thus, every study dealing with biological aspects of bone remodeling should take into consideration the mechanical aspect as well. With the same perspective, Pivonka et al. [82], have addressed the geometrical feedback effect upon bone volume evolution throughout the remodeling process and its capacity of accelerating osteoporotic porosity evolution. In this study, the osteoporosis origin has not been mentioned. Yet, its effect has been incorporated by increasing the PTH concentration by applying a continuous PTH administration rate of 500 pM/day, as previously done in [69], which induces an increase of RANKL/OPG's ratio and perturbs consequently its homeostatic steady-state.

Several other studies have been interested in osteoporosis effect on bone remodeling. For instance, [83, 84] are studies where the mechanobiological model developed by [80] has been modified to include PMO disease effect on bone remodeling process. RANKL production P_{RANKl} has been modified by adding the RANKL produced because of the PMO P_{RANKL}^{PMO} (Eq. (2)). This term leads to increase RANKL concentration and enhance preosteoclasts differentiation. The excess of RANKL production is defined by (Eq. (3)), where $P_{RANKL}^{PMO,ini}$ is PMO-initiating excess production rate of RANKL and φ_{PMO}^{RANKL} is reduced factor of $P_{RANKL}^{PMO,ini}$ which is

formulated as presented in (Eq. (4)). In (Eq. (4)), ξ represents the characteristic time of the RANKL production decrease, t_{PMO}^{RANKL} determine the shape of Lorentz-type function (Eq. (4)), and $t_{PMO,ini}$ the time corresponding to PMO onset.

$$P_{RANKl} = P_{RANKL}^{mech} + P_{RANKL}^{PMO} \tag{2}$$

$$P_{RANKL}^{PMO} = P_{RANKL}^{PMO,ini} \varphi_{PMO}^{RANKL} \tag{3}$$

$$\varphi_{PMO}^{RANKL} = \frac{\xi^2}{\xi^2 + \left(\frac{t - t_{PMO,ini}}{t_{PMO}^{RANKL}}\right)2} \tag{4}$$

Furthermore, PMO effect has been mediated by decreasing the anabolic strength parameter, as previously done in [80].

Recently, PMO problem has been further investigated in the mechanobiological model described in [85]. PMO effect has been incorporated while taking into consideration the mechanical loading applied on the bone. Indeed, the model mechanical aspect has been similar to the previous discussed work of [80] and PMO effect was incorporated in a similar way to the work [86], where authors have imposed an increase in RANKL concentration by including a dosage term that increases RANKL production. This term is derived from experimental data of ovariectomized rats.

6. Mechanobiological models treating bone healing and drugs effect

Mechanobiological mathematical models of bone remodeling are not only used to present diseases and mechanical effects on the process. Actually, the main target of all researchers, by developing these models, is to provide ideas and therapeutic solutions that could be applied in the real life after a clinical validation. Hence, in this section, some models considering bone healing and the effect of some bone diseases' treatments are discussed.

A mathematical model integrating the biological and mechanical aspects to describe the process of osteointegration has been described in [87]. The osteointegration is the direct structural and functional connection between a living bone and an artificial implant surface [88]. Knowing that many factors are involved into healing the interface between the non-biological material and bone, a mechanobiological modeling of the concerned surface is mandatory. In this study, authors have subdivided the bone healing process into four stages: (i) Blood clotting, (ii) Cell migration, (iii) Granulation tissue, and finally (iv) bone formation. The formulated mathematical model, describing the process, took into consideration all the stages of bone-implant healing. Yet, in this chapter, we have only shed the light on bone formation phase. Researchers have suggested a differential equation to schematize the osteogenesis stage, that depends on ontogenetic cells' migration and the osteogenic chemical variables. These two component values have been calculated based on previous equations describing the former phases. Concerning the mechanical stimulus, it has been presented through a displacement matrix.

In another study, authors have developed a mathematical bone remodeling model gathering the biological factors and the mechanical stimuli's effect on bone cells dynamics [89]. This research has been devoted to assess the bone mechanobiological response and the cellular activity variation over time depending on specific types of physical activities. Based on the previous works [88, 89], the bone cells concentrations have been calculated. The mechanical stimuli have been added to promote the proliferation of the preosteoblast and to regulate RANKL

production. As well as the majority of studies [80, 90, 91], the SED has been used to schematize the biomechanical stimuli's influence on cellular dynamics. The SED is calculated based on the stress and deformation tensors. In this study, these tensors were decomposed into deviatoric and hydrostatic parts, in order to get both hydrostatic and deviatoric SED quantities. Considering three stimuli in different remodeling periods, researchers have performed their finite element isotropic models. Seeking to know the formation performance, cortical and trabecular bone densities in the diaphysis and epiphysis regions of a proximal femur have been investigated. The comparison between the three mechanical stimuli (SED, deviatoric SED, and hydrostatic SED) revealed that: the formation of cortical and trabecular bone is higher for hydrostatic SED, followed by deviatoric SED, and finally by the whole SED stimuli. It has been remarked that the thickness of cortical bone was more significant applying Hydrostatic SED compared with the other stimulus type, while the trabecular density was higher under deviatoric SED stimulus. This study investigated then many mechanical stimuli and their particularity and effect on the development of bone density in many regions. Thus, it gave some insight about bone remodeling especially bone formation phase, which is also a primordial phase in bone healing process.

Concerning, the investigation of drugs dose effect on bone remodeling, the traditional mathematical models were not widely used in the literature. Instead, researchers opted for pharmacokinetic pharmacodynamic (PK/PD) models, which permit to predict the behavior of the treatment in different compartment of the body before reaching the blood. The results are then coupled with a traditional bone remodeling mathematical model. Various studies have been done in this respect, but which mostly treat the same type of drugs used for bone reparation such as denosumab. Studding denosumab effect on bone remodeling, this treatment has been generally included by modifying the function dedicated to calculate RANKL concentration in such a way the RANKL-binding denosumab is taken into consideration [82, 92]. In the work of [83], the mechanobiological feedback function has been incorporated to regulate preosteoclasts proliferation as previously done in [80] and the denosumab effect has been added by adjusting RANKL concentration. Other studies have been interested in PTH drug's effect, which is usually used for postmenopausal women. In the work of [86] for example, authors have created an equation representing PTH amount in the blood depending on the serum concentration injected. Based on the outcomes, they formulated another function that will control preosteoblast proliferation, lining cells differentiation, and active osteoclast apoptosis. Another recent study [85] has been based on [86], have investigated the same thing, which is PTH effect on bone density. This time, authors have included PTH into their bone remodeling mathematical model by modifying active osteoblasts apoptosis rate multiplying the normal parameter value by the function representing PTH drug concentration. In contrary to the work of [86], this model considered the mechanical feedback triggering preosteoblast proliferation. The term representing this mechanical feedback is the same used in [80].

7. Conclusion

To maintain the multiple functions of a skeletal, this last should be regularly renewed in such a way the old bone tissue is substituted with a new one. Applying cyclic mechanical loading on the bone helps to trigger the bone remodeling. Thus, people doing physical activities generally have stronger bones. On the other hand, the occurrence of some diseases because of age, hormonal deficiency or bad dietary habits leads to bone deterioration. The present chapter shed the light on the most

popular bone diseases and the different mechanobiological bone remodeling that investigate the evolution of these diseases and some drugs effect on the evolution of bone mass over time. Based on the forgoing reviewed articles, some conclusions could be extracted:

- Further studies should be elaborated to treat additional bone diseases effect on bone, especially the prostate and breast cancer.
- Further studies should be elaborated to treat several drugs effect on bone repairing such as bisphosphonates and estrogen drugs.
- The mechanical aspect is extremely important while investigating the bone remodeling process as bone is always in touch with the external environment and the loading effects are not negligible.

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Conflict of interest

The authors declare no conflict of interest.

Author details

Imane Ait Oumghar[1,2*], Abdelwahed Barkaoui[2] and Patrick Chabrand[1]

1 Aix Marseille Univ, CNRS, ISM Inst Mouvement Sci, Marseille, France

2 Laboratoire des Energies Renouvelables et Matériaux Avancés (LERMA), Université Internationale de Rabat, Rabat-Sala El Jadida, Morocco

*Address all correspondence to: imane.aitoumghar@uir.ac.ma

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