



Inflammation, Oxidative Stress, and Bone in Chronic Kidney Disease in the Osteoimmunology Era

Sandro Mazzaferro^{1,2} · Domenico Bagordo¹ · Natalia De Martini¹ · Marzia Pasquali² · Silverio Rotondi³ · Lida Tartaglione¹ · Peter Stenvinkel⁴ on behalf of the ERA-EDTA CKD-MBD working group

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Abstract

Bone is not only a mineralized and apparently non-vital structure that provides support for locomotion and protection to inner organs. An increasing number of studies are unveiling new biologic functions and connections to other systems, giving the rise to new fields of research, such as osteoimmunology. The bone marrow niche, a new entity in bone physiology, seems to represent the site where a complex crosstalk between bone and immune/inflammatory responses takes place. An impressive interplay with the immune system is realized in bone marrow, with reciprocal influences between bone cells and haematopoietic cells. In this way, systemic chronic inflammatory diseases realize a crosstalk with bone, resulting in bone disease. Thus, pathogenetic links between chronic kidney disease-mineral bone disorders and osteoporosis, cardiovascular disease, and ageing are common. The aim of this narrative review is to provide a general view of the progresses in the field of bone research and their potential clinical implications, with emphasis on the links with inflammation and the connections to osteoimmunology and chemokines.

Keywords Bone physiology · Bone marrow niche · Osteoimmunology · Chronic kidney disease · Chemokines · CKD-MBD

Introduction

Until recently, bone has been regarded as the pillar of human body, providing support for locomotion and protection to inner organs. However, this old-fashioned view of a mineralized and thus non-vital structure of body (capable of surviving for ages to the death of all other organs) needs to be updated. Recent years are witnessing a dramatic increment of our knowledge of the biologic role of bone. An increasing number of biochemical and hormonal pathways are revealed and bone functions can now be extended over

the classical role of calcium and phosphate homeostasis to wide endocrine effects. Moreover, ongoing research on the association with the immune system is of such interest that a nickname has been coined to identify this new field: osteoimmunology [1].

Similarly, in recent years, a new role is emerging for chronic kidney disease (CKD) which is appreciated as an increasingly prevalent disease affecting some 700 million subjects in the world [2] and as a significant risk factor for overall and cardiovascular morbidity and mortality [3, 4]. Renal failure typically associates with a specific bone disease, generally indicated as renal osteodystrophy (ROD), which includes some different histologic figures. Together with the biochemical derangements of secondary hyperparathyroidism and the pathogenetically associated vascular and ectopic calcifications, bone lesions of renal patients have been included into a new clinical entity, named chronic kidney disease-mineral bone disorders (CKD-MBD) which could be tentatively regarded as a new syndrome [5, 6], part of a premature ageing process in the uremic milieu [7], that could help explain at least some of the heavy prices payed by renal patients in terms of morbidity and mortality. As a consequence, renal failure, with the associated secondary

✉ Sandro Mazzaferro
sandro.mazzaferro@uniroma1.it

¹ Department of Translational and Precision Medicine, Sapienza University of Rome, Viale del Policlinico, 155, 00161 Rome, Italy

² Nephrology Unit, Policlinico Umberto I, Rome, Italy

³ Nephrology and Dialysis Unit, ICOT Hospital, Polo Pontino Sapienza University of Rome, Rome, Italy

⁴ Division of Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden

bone lesions, becomes involved into a wider, extrarenal and systemic, clinical picture. Therefore, a deep understanding of the biologic role played by bone becomes necessary in order to recognize new pathways that underlie these links and could improve our diagnostic and therapeutic strategies. In particular, bone niche, a new entity in bone physiology, represents the site where bone cells and bone marrow cells come into contact with each other and exchange signals, realizing the crosstalk between bone and immune/inflammatory response.

The aim of this narrative review is to provide a general view of the progresses occurring in the field of bone research, with emphasis on the links with inflammation. For this purpose, we will briefly update the process of bone remodelling, novelties on bone marrow niche, and the connections to osteoimmunology and chemokines. Finally, the potential clinical implications will be explored.

Bone Remodelling

Bone undergoes a complex remodelling cycle, classically divided into four different phases. In the “latent phase”, osteocytes activate bone-lining cells which activate the process of osteoclast differentiation, ending up with the exposure of bone surface. Then, during the “activation phase”, osteoclasts resorb the exposed bone and then detach and die via apoptosis. At this point, the “reverse phase” takes place where macrophage-like cells, migrating to the resorbed lacuna, clean debris, and secrete stimulating factors. Attracted by these factors, osteoblasts occupy the lacuna and fill it up with organic osteoid matrix during the “formation phase”. The matrix mineralizes while osteoblasts either undergo apoptosis or become embedded in the bone matrix. They can turn into bone-lining cells or continue their differentiation to become mature osteocytes [8]. The whole remodelling cycle may last months [9]. Importantly, during these phases, bone cells undergo a complex differentiation process, passing through several stages and many phenotypic transformations, with different function and metabolic needs. In more details, osteoclasts originate from haematopoietic stem cells (HSCs) of the monocyte/macrophage lineage. In this stage, osteoblast-derived cytokines like macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL) are necessary to promote osteoclasts differentiation. In particular, M-CSF stimulation leads to osteoclast-precursors proliferation while the terminal differentiation is favoured by RANKL [10, 11]. Osteoblast formation is comparably complex and requires the action of growth factors and hormones like parathyroid hormone (PTH) and Wnt-related integration sites (Wnt) proteins. On the other hand, osteoblast precursors originate from pluripotent mesenchymal stem

cells (MSCs) and their progressive differentiation is guided by further different molecules. Among these, Wnt10b is one of the most relevant, also inhibiting the possibility for mesenchymal cells to differentiate into adipocytes and other cell types (chondroblasts, myoblasts, fibroblasts, etc.) [8]. All these cells originate from similar precursors while their fate is influenced by other factors, such as cytokines, hormones, and transduction signal pathways. Impressively, the number of differently shaped elements that can be recognized in the human skeleton is > 200 [8]. It is thus evident that bone marrow is populated by a wide range of undifferentiated precursors of bone mature cells, in close physical contact with other undifferentiated cells of haematologic interest. It is noteworthy that the study of different bone diseases is assigned to different specialist doctors: haematologists for bone marrow, orthopaedics for mechanical functional disturbances, and nephrologists, endocrinologists and internists for bone metabolism. However, since it is becoming evident that there is an important crosstalk between bone cells and immune cells with possible systemic and endocrine-like effects, an increased level of communication among these specialists should be encouraged. Recent discoveries indicate that a point of union could exist at the level of the bone marrow niche.

Bone Marrow Niches

The term niche is used to identify a microenvironment in an anatomic site. This microenvironment includes stem cells whose fate is regulated by the composition of the surrounding tissue. Conceptually, stem cell division can be either symmetric (giving rise to two identical pluripotent cells) or asymmetric (producing one pluripotent and one multipotent cell). The first type of division guarantees the reservoir of stem cells for any further kind of differentiation, while the second gives origin to cells that can differentiate into a limited family-related type of multipotent cells. In the bone marrow, the niche hosts HSCs, providing them with structural and functional support for proliferation, differentiation, and mobilization. These cells are located in two different areas: one in the endosteal bone surface in proximity of osteoblasts (“*osteoblastic niche*”) and one in the vessel pole of bone marrow (“*vascular niche*”) [12]. Under physiologic conditions, HSCs can leave the endosteal niche and move towards the pole of endothelial sinusoidal vessel cells. During this migration, they further differentiate into more specific but less potent haematopoietic cells. The movement from one niche to the other is driven by the microenvironment resulting from different concentrations of variable cytokines (“chemotactic gradients”). A complex interplay of signalling and adhesion molecules occurs among which, besides acronyms of metabolic pathways (e.g. SCF/c-Kit,

Jagged/Notch, Ang-1/Tie2, etc.), we can find that PTH, Vitamin D, and Ca^{2+} -sensing receptors (CaSR) are involved. In addition, higher oxygen concentrations, growth factors (e.g. FGF-4 in the vascular niche), and pH contribute to HSC recruitment and proliferation [13]. When HSCs reach the vascular niche, they can spill into the bloodstream and move towards target organs, like thymus or nodes, to complete their maturation and function. Importantly, HSCs can also return to the endosteal niche in an opposite process called “homing”. Therefore, the fate of HSCs in the bone marrow is governed by biochemical and physical gradients that allow the two processes of migration towards extraosseous tissues and homing [14]. Increasing knowledge in bone niches allowed to recognize that also osteoclasts and osteocytes are involved in the function of osteoblastic niche, which is currently identified, more generically, as “*endosteal niche*”. Further, the presence of a third niche, located between the other two and characterized by the presence of a specific cell type, the so-called CXC-chemokine ligand 12 (CXCL12)-abundant reticular (CAR) cells (see below), is recognized and named “*reticular niche*” [15]. CAR cells can be either osteoprogenitor or play a major role in homing, retention, and repopulation of HSCs. In conclusion, bone marrow hosts a number of complex and fascinating hubs constituted by cell types exchanging transduction pathways activating signals, linked by structural and functional interactions named bone niches, which are graphically summarized in Fig. 1. A complete understanding of their biologic functions is warranted.

Osteoimmunology

According to recent findings, beside its classical structural (locomotion, protection of vital organs, and weight bearing) and metabolic roles in calcium-phosphate homeostasis, bone is relevant in glucose metabolism, energy expenditure, male fertility, and cognitive functions. The deep connection with the immune system is now giving rise to a completely new field of research, named *osteoimmunology*, which mainly focuses on the relation between bone cells and immune cells [16]. This term was initially adopted by Arron and Choi [1], who showed the relation existing between immune and bone cells.

We know that immune-related mediators, like interleukins (e.g. IL-6, IL-11, IL-17, IL-23), tumour necrosis factor (TNF), receptor activator of nuclear factor kappa-B (RANK), RANKL, nuclear factor of activated T cells, cytoplasmic-1 (NFATc1), and other molecules produced by immune cells are capable of modulating bone cell biology. The novelty is that also bone cells regulate immunocompetent bone marrow cells. In fact, osteoblasts regulate commitment and differentiation of B cells through different

signalling and transduction pathways. Osteoclasts, by acting on the niche, reduce HSCs homing through production of specific molecules [16] and might also be part of the inflammatory response since they have a role in presenting antigens, activating T cells, and modulating immune response. As for osteocytes, with their peculiar dendritic shape, they can have both direct interaction with HSCs and indirect influence through release of soluble factors that regulate the activity of a number of cells in the niche, like endosteal osteoblasts, osteoclasts, and CAR cells [17]. It is therefore evident that bone cells affect the function of bone niche and the destiny of undifferentiated stem cells, thus influencing the inflammatory and immune responses.

The Role of Chemokines

Among the recent discoveries on the biology of bone niche, the role played by chemokines deserves a special mention. Chemokines belong to the cytokines family and take their name from their ability to induce chemotaxis in selected cells. These signalling proteins, with a molecular weight ranging between 8 and 12 kDa, regulate migration, localization, and function of immune cells. Two major chemokine subgroups are recognized as follows: the Cys–Cys adjacent residues Chemokines (or C–C Chemokines, including 27 different molecules and 10 different C–C Receptors), and the Cys–X–Cys Separated Residues Chemokines (C–X–C Chemokines, with 17 different molecules and 7 different C–X–C Receptors) in which 1 or 2 amino acids separate the two adjacent Cys residues. A comprehensive description of chemokines and their functions is beyond the scope of this review, but it is worth mentioning those functions that are known to influence both niche environment and bone remodelling.

Chemokines are major regulators of the chemotactic gradients that favour migration of undifferentiated cells within bone marrow niches. Thus, chemokine signalling deeply influences the activity of bone marrow niche, bone formation, and resorption. Specific chemokines activate or inhibit either bone formation or resorption [18]. However, their biologic role is variable, as evidenced by two transgenic animal models. For example, the CCL5 chemokine is known to stimulate bone formation and to reduce bone resorption, and in CCL5, null mice osteoblast and bone-lining cells are not present on the endocortical surface at birth. The phenotype is not lethal and, intriguingly, it disappears completely with growth clearly indicating the functional redundancy of this chemokine. On the other site, transgenic mice null for either CXCL12 or for its receptor CXCR4, die prenatally, indicating a much more relevant biologic role. This chemokine and its receptor are abundantly expressed by a specific reticular type of multipotent cells in the bone marrow, now identified

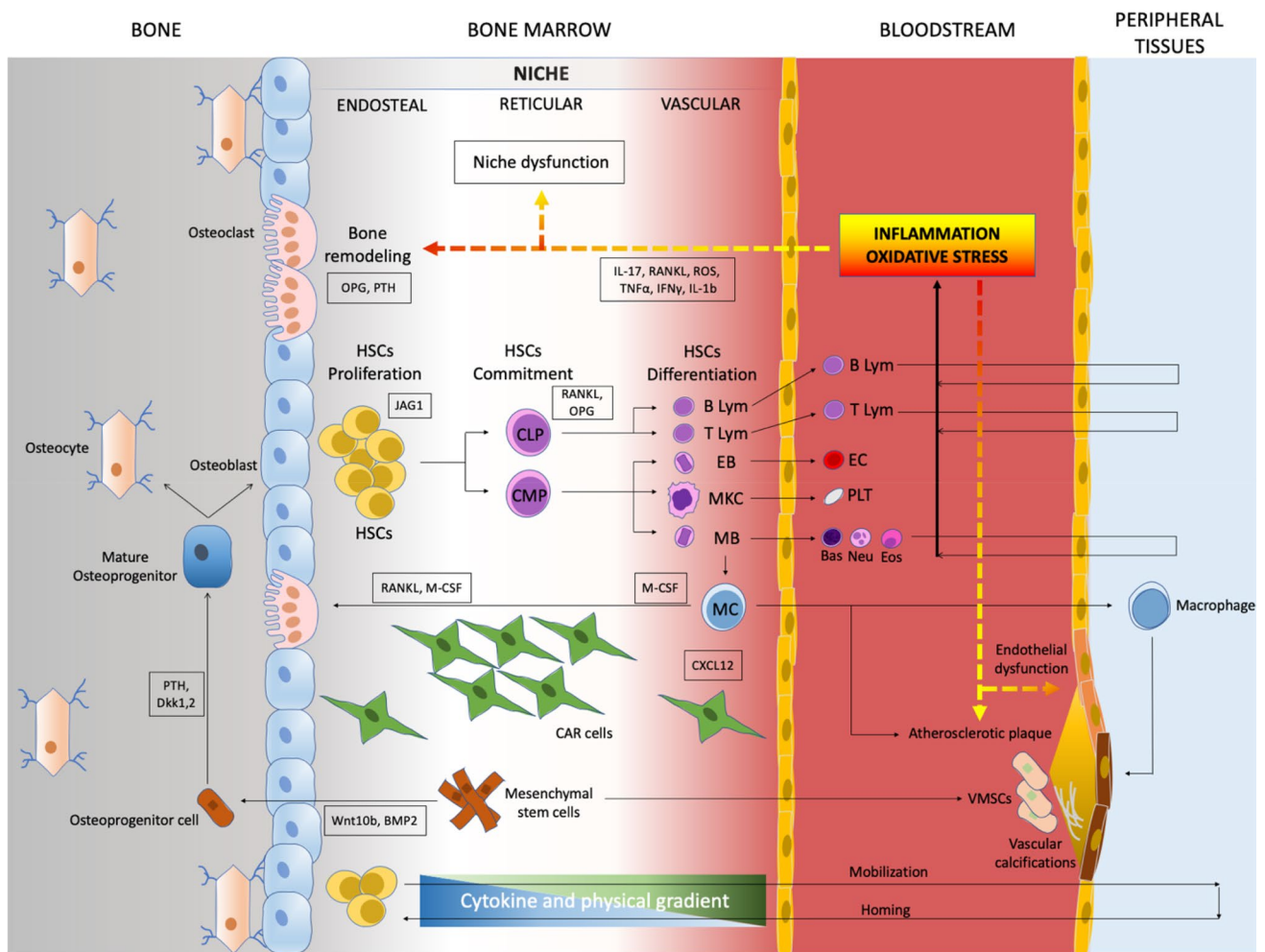


Fig. 1 Endosteal, reticular, and vascular niches in the context of bone marrow. In the endosteal niche, HSCs proliferate and, while their number increases, they move toward the vascular niche following cytokine and physical gradient (mobilization) and reaching the vascular niche, where further differentiation into mature elements occurs. HSCs differentiation leads to cell types, including monocytes, which can turn into osteoclasts or macrophage. Monocytes and macrophages can then move to peripheral tissues through systemic vessels. HSCs homing is favoured by CXCL12 produced by CAR cells, particularly abundant in reticular niche. In bone marrow niche, mesenchymal stem cells can be found, which under the influence of Wnt10b and BMP2 are able to move to bone matrix and differentiate into osteoblasts. B Lym B lymphocyte, Bas basophil,

BMP2 bone morphogenetic protein 2, CAR cells CXCL12-abundant reticular cells, CLP common lymphoid progenitor, CMP common myeloid progenitor, CXCL12 CXC-chemokine ligand 12, Dkk1,2 Dickkopf Wnt signalling pathway inhibitor 1,2, EB erythroblast, EC erythrocyte, Eos eosinophil, HSCs haematopoietic stem cells, IFN γ interferon- γ , IL1b interleukin-1b, IL-17 interleukin-17, JAG1 jagged1, MB myeloblast, MC monocyte, M-CSF macrophage colony-stimulating factor, MKC megakaryocyte, Neu neutrophil, OPG osteoprotegerin, PLT platelet, PTH parathyroid hormone, RANKL receptor activator of nuclear factor kappa-B ligand, ROS reactive oxygen species, T Lym T lymphocyte, TNF α tumour necrosis factor- α , VMSCs vascular smooth muscle cells, Wnt10b Wingless-related integration sites proteins 10b

as CAR cells (CXCL12-abundant reticular cells), which are considered as major cellular elements of the aforementioned third bone marrow niche, or “reticular niche”. CXCL12 is essential for homing and retention of HSCs, affects bone resorption and formation, promotes angiogenesis, pre-osteoclasts recruitment and commitment, and has been associated with tumour-induced osteolysis [18].

As a whole, bone is the container of many different cell types (HSCs, dendritic cells, endothelial cells, osteoblasts, osteoclasts, osteocytes, adipocytes, neurons, mesenchymal

cells, macrophages, T- and B-lymphocytes) surrounded by a number of extracellular bone matrix proteins (fibroblast growth factors, bone morphogenetic proteins, etc.) which are bathed by a variety of cytokines—ILs, TNF, transforming growth factor (TGF)- β , etc.—and are capable of receiving neuronal, mechanical, and physical (pH, oxygen) stimuli. The resulting bone marrow microenvironment drives the fate of HSCs and bone cells. We can imagine bone as a sophisticated inner sensor which receives different inputs (diet, exercise/gravity, stress, infections, etc.) and reacts in

order to induce endocrine, immune, and nervous adaptive responses [15].

Clinical Implications

Bone and Inflammation

The discovery of bone niches and their biologic roles raises the question of possible reciprocal relationships with bone diseases, inflammation, oxidative stress, and immune response. Indeed, the role of systemic inflammation in bone cells activity is now evident in autoimmune diseases. For example, during the initiation phase of rheumatoid arthritis, naïve T cells, stimulated by environmental and genetic factors, differentiate into T-helper 17 (Th17) cells, which then play a pivotal role in inducing and sustaining the bone lesions typical of this disease through IL-17 secretion. Increments in IL-17 lead to progression towards the inflammatory phase of the disease, generation of the synovial pannus, increased RANKL expression on mesenchymal cells, osteoclast recruitment, and bone resorption and destruction [15]. Similarly, in any infection-related inflammation, following the antigen presentation by macrophages or dendritic cells, naïve T cells proliferate and turn into different subsets, among which Th17 cells which express RANKL and, by producing great amounts of IL-17, induce RANKL expression on synovial fibroblasts and osteoblasts, thus promoting osteoclastogenesis. Other mediators like interferon- γ , IL-4, and IL-10, produced by other subsets of T cell (Th1 and Th2), together with the osteoprotegerin (OPG) produced by B cells, inhibit osteoclast formation and differentiation. Therefore, the cytokine increment produced by immune cells interacts with osteoblasts and osteoclasts, affects bone remodelling, and determines the extent of bone erosion during inflammatory responses [19].

In a common clinical condition like osteoporosis, mechanical unloading and/or underlying diseases stimulate the production of several cytokines and inflammatory mediators, such as IL-6, TGF- α , Insulin-like growth factor (IGF)-1, which in turn promote an increase in RANKL, M-CSF, and monocyte chemoattractant protein 1 (MCP-1), and downregulate OPG expression, resulting in osteoclast differentiation/activation and, finally, in bone remodelling impairments. Furthermore, age-related osteoporosis is currently regarded as an autoimmune disease [20]. Osteoporosis may also occur in both infancy and adulthood secondary to interactions between bone and muscles. An example is given by the “disuse osteoporosis” of children with cerebral palsy who develop the disease during skeletal development [21]. In adult age, muscle paralysis activates, through complex and still poorly understood pathways, a rapid immune response which is followed by RANKL-mediated osteoclastogenesis

and acute trabecular bone loss [22]. In animal models, this transient acute inflammatory response induced by muscle paralysis leads to the generation of giant osteoclasts likely responsible of the severe bone derangements observed in this condition [23]. Interestingly, in murine models of Duchenne muscular dystrophy, anti-RANKL agents (now available as a drug) inhibited nuclear factor kappa-B pathway and improved both the mechanical properties of bone and the skeletal muscle performance [24]. Therefore, the interplay between muscle disease, skeleton, and inflammation provides insights in bone physiology and unveils new possible therapeutic targets.

Sickness Behaviour

To understand the relationship between systemic inflammation and bone, it may be useful to watch at the inflammatory response from an evolutionary point of view. Inflammation is undoubtedly a conservative, defensive response aiming at facing external injuries and at restoring the basal condition. Besides the local effects, inflammation is also capable of inducing the so-called sickness behaviour by a complex neuro-endocrine reprogramming of activities. Symptoms like fatigue, malaise, and anorexia ensue and may seem detrimental, but are actually finalized at sparing energy that is now required for the immune response. Also, in settings of presumably reduced access to nutrients (e.g. for reduced mobility), the accessibility to vital ions like calcium could be limited and, therefore, the inflammatory process mobilizes calcium from bone by increasing bone resorption [25]. In this way, acute, short-term inflammatory episodes result in bursts of bone loss that will be recovered after resolution of the underlying disease. However, in case of a chronic, long-lasting inflammatory state, this defence mechanism becomes maladaptive and may lead to negative calcium balance and osteopenia. Any long bone fracture can be regarded as an acute inflammatory state associated with cytokine secretion and some degree of sickness behaviour, favouring rest and bone healing. Similarly, microscopic fractures (microcracks) physiologically happening in bone promote remodelling and lead to bone renewal by activating the local production of cytokines. However, if microcracks are numerous, repetitive, and diffuse, they become responsible for a chronic smouldering state of inflammation that, more than guiding towards repair, contributes to develop osteopenia and osteoporosis [26].

Inflammaging

It is interesting to notice that ageing is recently regarded as a chronic systemic inflammatory condition, nicknamed “inflammaging”, and characterized by metabolic dysregulation and the increase of several inflammatory biomarkers

[27] and downregulation of the cytoprotective transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of antioxidant responses [28]. Mechanisms involved in the pathogenesis of “inflammaging” are multiple and, beside repressed Nrf2 expression, include mitochondrial dysfunction, senescence, tissue hypoxia, oxidative stress, intrinsic immune cell defects, and changes in gut microbiome [29]. The “inflammation” diseasome, which embraces clinical conditions like cardiovascular disease, type 2 diabetes, CKD, anaemia, sarcopenia, cancer, and neurologic dysfunctions like depression and dementia, is often accompanied by osteopenia and osteoporosis [30]. The constant buzz of internal activation in “inflammaging” renders immune cells less responsive and predisposes patients with “inflammaging” to infectious complications, such as COVID-19 [31]. Thus, a derangement in bone niche function interfering with the intense crosstalk between immune cells and bone cells is likely.

CKD-MBD and Nrf2

An important role of Nrf2 in the calcification process has been increasingly appreciated due to its major regulatory functions in the antioxidant and anti-inflammatory pathways [32]. Recent experimental animal studies have demonstrated a major role of Nrf2 in the vascular calcification process [32]. Thus, the classic Nrf2 activator, dimethyl fumarate attenuated vascular calcifications under hypercalcemic and hyperphosphatemic conditions in mice [33] and sodium hydrosulfide (a H₂S donor) ameliorates calciprotein particle-induced calcification in vitro through the activation of the Nrf2 system [34]. Accumulating evidences also support a role of Nrf2 in bone disease. Since Nrf2 deletion results in an increased expression of Runt-related transcription factor 2 (RUNX2) [35] and Nrf2 was shown to be a regulator of osteoclastogenesis and pathological bone erosion [36], a role of Nrf2 for bone regeneration in pathological fractures has been proposed [37]. Thus, translational pre-clinical and clinical studies addressing the targeting capabilities of Nrf2 agonists to prevent vascular calcification and bone loss would be of interest in the context of CKD-MBD.

CKD, CKD-MBD, Inflammation, and Ageing

CKD patients typically suffer from both a peculiar type of bone disease, named ROD, and a chronic inflammatory state [38, 39], suggesting that bone niche could be possibly involved in either a passive or active role. As abovementioned, the impaired metabolism of divalent ions in CKD is now recapitulated into a specific clinical entity named CKD-MBD to embrace the biochemical abnormalities of secondary hyperparathyroidism, the disorders of bone turnover, mineralization, and volume as well as the associated

vascular and soft tissue calcifications, as a whole resulting in increased risks of cardiovascular and overall mortality [5]. CKD-MBD seems to start very early in CKD and some derangements are particularly claimed to play a role: phosphate metabolism, adynamic bone disease, fibroblast growth factor 23 (FGF23), and Klotho secretion. Dietary phosphate load, with or without hyperphosphatemia, is a recognized risk factor for cardiovascular disease and mortality [40], associated with vascular calcification, endothelial dysfunction, left ventricular hypertrophy, and anaemia in CKD patients [41]. FGF23, whose levels increase in early stages of CKD [42], is mainly produced by osteocytes and is renowned for its prominent regulatory role in vitamin D and mineral metabolism [43–45]. However, other systemic effects are appreciated, among which induction of myocardial hypertrophy through the activation of a specific receptor [46] increased synthesis of inflammatory cytokines [47] and inhibition of neutrophil recruitment during inflammation [48]. FGF23 is deeply linked with its co-receptor Klotho, which is currently considered as an anti-ageing protein [49]. Synthesized by kidneys, Klotho levels are progressively reduced along with the reduction of glomerular filtration rate since the very early stages [50]. For this reason, renal failure is regarded as a possible example of Klotho-deficiency status, resulting in poorer survival rate. Finally, low turnover or adynamic bone is frequently observed in CKD and could probably represent the first bone derangement occurring of CKD progression [51, 52]. The pathogenesis of adynamic bone is not completely understood but could be secondary to bone resistance to PTH, dysregulation of vitamin D synthesis, increased production of sclerostin, and Dickkopf-1 protein (DKK1) by osteocytes and osteoblasts, respectively. Adynamic bone impairs bone buffering capacity for phosphate and calcium but is also expected to delay microfractures healing. Observational data describe its association with vascular calcifications, bone fractures, as well as morbidity and mortality [53].

In more advanced stages of CKD, protein-bound uremic toxins could be responsible for bone disease. One of these indoxyl sulphates, whose levels are sky-high in dialysis patients, plays a key role in bone cell metabolism by reducing osteoclast differentiation and inducing osteoblast apoptosis [54]. Furthermore, in vitro studies demonstrated that high levels of indoxyl sulphate may reduce PTH-stimulated cyclic adenosine monophosphate (cAMP) and PTH receptors in bone cells [55]. These findings suggest that indoxyl sulphate may represent a key factor of adynamic bone and low bone turnover, secondary to bone resistance to PTH. Moreover, in experiments on human renal proximal tubular cells, high levels of indoxyl sulphate increased free radicals synthesis and oxidative stress [56].

Another point to consider in CKD is that PTH lowering therapy could have beneficial effects. In fact, several reports

highlighted that vitamin D receptor activators and calcimimetics are effective in reducing oxidative stress markers [57, 58] and similar results were described after parathyroidectomy [59], thus indicating that new targets could be considered in the management of CKD-MBD.

Since renal patients and elderly people share several clinical features (e.g. bone demineralization, vascular calcifications, increased susceptibility to infection, cardiovascular disease, and increased mortality rate), CKD could be seen as a clinical condition of accelerated ageing [60]. By analogy, given the involvement of CKD-MBD with the development of all the abovementioned features of ageing, it has been suggested that early metabolic modifications of CKD-MBD could similarly act in the process of ageing and might thus represent a reference model of accelerated ageing. If ROD or, more in general CKD-MBD, also influences the biologic function of bone niche is still unknown. As a matter of fact, many biomarkers of CKD-MBD affect the crosstalk of bone, bone marrow, and vessels, which seems necessary to maintain the physiologic role of the niche. In particular, we know that PTH, PTH receptor, FGF23 and its receptor, Vitamin D and its receptor, as well as CaSR are all involved in the regulation of HSCs fate. For example, PTH guides HSCs expansion and mobilization/homing by acting directly on osteoblasts by a receptor-mediated way and indirectly via induced molecules (NotchL/Jagged1, granulocyte colony-stimulating factor) that regulate CXCL12 and ILs expression; calcitriol favours MSCs differentiation into osteoblasts, and CaSR expression on HSCs is required for their settlement in the bone marrow [26]. Recently, in an experimental model of CKD-MBD, niche dysfunction was evidenced by the presence of increased number of immature colony-forming units in peripheral blood and spleen, significant decrease of HSCs in bone marrow and impaired long-term repopulation potential, macrophage function, and B-lymphopoiesis [61].

In summary, according to recent discoveries, bone can be regarded as a sophisticated inner sensor, deeply connected with immune-inflammatory responses and linked to a great number of other systemic functions with possible pathogenetic links with osteoporosis, CKD-MBD, cardiovascular disease, and premature ageing. Bone marrow niches represent new functional units that could help explain the physiologic links between bone and the systemic response to inflammation. Also, it is relevant to discover if bone diseases are responsible for niche dysfunction and/or vice versa. Conceivably, and interestingly, new drugs capable of modifying signal pathways in the bone niche could also affect the natural process of ageing.

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Compliance with Ethical Standards

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