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REVIEW

The impact of inflammation on bone mass in children

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Abstract Bone is a dynamic tissue. Skeletal bone integrity is maintained through bone modeling and remodeling. The mechanisms underlying this bone mass regulation are complex and interrelated. An imbalance in the regulation of bone remodeling through bone resorption and bone formation results in bone loss. Chronic inflammation influences bone mass regulation. Inflammation-related bone disorders share many common mechanisms of bone loss. These mechanisms are ultimately mediated through the uncoupling of bone remodeling. Cachexia, physical inactivity, pro-inflammatory cytokines, as well as iatrogenic factors related to effects of immunosuppression are some of the common mechanisms. Recently, cytokine signaling through the central nervous system has been investigated for its potential role in bone mass dysregulation in inflammatory conditions. Growing research on the molecular mechanisms involved in inflammation-induced bone loss may lead to more selective therapeutic targeting of these pathological signaling pathways.

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Introduction

Chronic inflammation influences bone mass regulation [1, 2]. The mechanisms underlying this bone mass regulation are complex and interrelated. Inflammation disorders, such as rheumatoid arthritis and inflammatory bowel disease, share many common mechanisms but also have unique features of bone mass dysregulation [1–4]. These mechanisms are ultimately mediated through the regulation of bone modeling and remodeling cycle [5, 6].

Bone modeling and bone remodeling

Bone is a dynamic tissue designed to provide structural support and an important reservoir for mineral and hematopoietic cells [3]. Bone modeling adapts structure to loading by changing bone size and shape and so maintains bone strength [7]. Bone modeling is the sum of the activities of the endosteum and periosteum of bone to produce bone forms [8]. Bone modeling predominates during growth [9]. Bone formation and resorption are not coupled in time or space in skeletal modeling. This process results in an increase in bone diameter and modification of bone shape. Bone modeling results in new bone formed at a location different from the site of bone resorption [10]. Adolescence has been associated with accelerated bone maturation and bone modeling is responsible for approximately 40% of peak skeletal mass [11]. Bone modeling is important for changes in cortical geometry during growth.

Peak bone mass occurs toward the end of the third decade of life [12].

On the other hand, bone remodeling (or bone metabolism) is a life-long process where old bone is removed from the skeleton and new bone is added. Remodeling is initiated by damage-induced osteocyte apoptosis, which signals the location of damage via the osteocyte-canalicular system to endosteal lining cells that form the canopy of a bone remodeling compartment [7]. These processes also replace bone during growth and following injuries like fractures but also micro-damage, which occurs during normal activity. Remodeling responds to functional demands of the mechanical loading. As a result, bone is added where needed and removed where it is not required. Molecular signaling within the bone remodeling compartment between precursors, mature cells, cells of the immune system, and products of the resorbed matrix titrate the birth, work, and lifespan of this remodeling machinery to either remove or form a net volume of bone.

Bone modeling and remodeling processes are not very different at the cellular level. They are based on the separate actions of osteoclasts and osteoblasts. A full remodeling cycle is comprised of bone removal, or resorption, by osteoclasts followed by bone formation by osteoblasts, two processes that are tightly coupled. A schematic view of bone remodeling process is illustrated in Fig. 1. The active process of bone accumulation, or bone mass, is dependent on bone volume, height, and puberty in childhood [11]. The rate of bone remodeling is much higher in growing children [13]. In the first year of life, almost 100% of the skeleton is replaced. In adults, remodeling proceeds at about 10% per year. Both osteoclasts and osteoblasts are derived from their progenitors that reside in the bone marrow. Osteoclastogenesis is dependent on an adequate microenvironment, which provides essential signals such as macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB (RANKL) and cytokines [7, 14]. Osteoblasts are cells of mesenchymal origin that are responsible for bone formation by secreting bone matrix proteins and promoting mineralization. Differentiated osteoblasts embedded in the bone matrix are termed osteocytes, and they have an important function within bone as mechanosensors and initiate bone remodeling [5]. Pre-osteoblasts express M-CSF and RANKL and can induce osteoclast formation, indicating the close interaction between bone formation and bone resorption [5, 14].

The identification of the RANKL-RANK-osteoprotegerin (OPG) system is a major breakthrough in bone biology. Disruption of the RANKL-RANK-OPG axis leads to the uncoupling of bone metabolism [2]. RANKL enhances differentiation of osteoclasts and their bone resorption capacity [15]. Several osteotropic factors, including vitamin D, parathyroid hormone (PTH) and prostaglandins promote the expression of RANKL [1, 2]. The Wnt genes encode a highly conserved class of signaling factors required for the development of musculoskeletal and neural structures. Wnt signaling is critical for bone mass accrual, bone remodeling, and fracture repair [1, 16–19].

Uncoupling of the bone remodeling cycle in chronic inflammatory disorders

Bone remodeling process regulates calcium homeostasis, repairs micro-damaged bones from everyday stress, and also shapes and ensures the mechanical integrity of the skeleton throughout life [3–5, 7]. An imbalance in the regulation of bone remodeling's two contrasting events, bone resorption and bone formation, results in bone loss. Chronic inflammatory diseases in children negatively influence skeletal health. Inflammation-associated bone loss can lead to growth retardation, reduced peak bone mass, and increased fracture risk [20]. Various mechanisms have been proposed for bone loss during inflammation [10]. The underlying disease process or therapeutic agents such as immunosuppressive therapies may influence bone cell function in inflammatory disorders.

Chronic inflammatory diseases are often associated with cachexia [21, 22]. Cachexia is associated with anorexia and reduced nutritional intake and negatively impacts bone mass [23]. Chronic inflammation of the gastrointestinal tract reduces calorie intake and inhibits the absorption of nutrients important to bone metabolism [1]. Mildly elevated plasma homocysteine levels induced by vitamin B insufficiency deteriorate normal collagen cross-link formation, an important bone quality determinant [24, 25]. Furthermore, vitamin D deficiency is often prevalent in chronic inflammatory diseases [26]. Vitamin D deficiency reduces calcium and phosphorus absorption, increases PTH secretion, and enhances RANKL expression on osteoblasts [27]. Elevated expression of RANKL enhances bone resorption by promoting osteoclastogenesis. Vitamin D deficiency causes growth retardation and skeletal deformities in children [28]. In adults, vitamin D deficiency exacerbates osteopenia and osteoporosis, causes osteomalacia, and muscle weakness. Vitamin D can also modulate the immune response, and thus exerts an indirect role in inflammation-associated bone loss [29].

Physical immobility associated with chronic inflammatory conditions can lead to bone loss through reduced mechanical bone stimulation. Local or systemic inflammation causes pain, spasm, and decreased flexibility. Prolonged physical inactivity contributes to bone loss. Bone grows in response to the magnitude and direction of the forces to which it is subjected [10, 30]. This response keeps mechanically induced deformation of bone at a set point. Physical

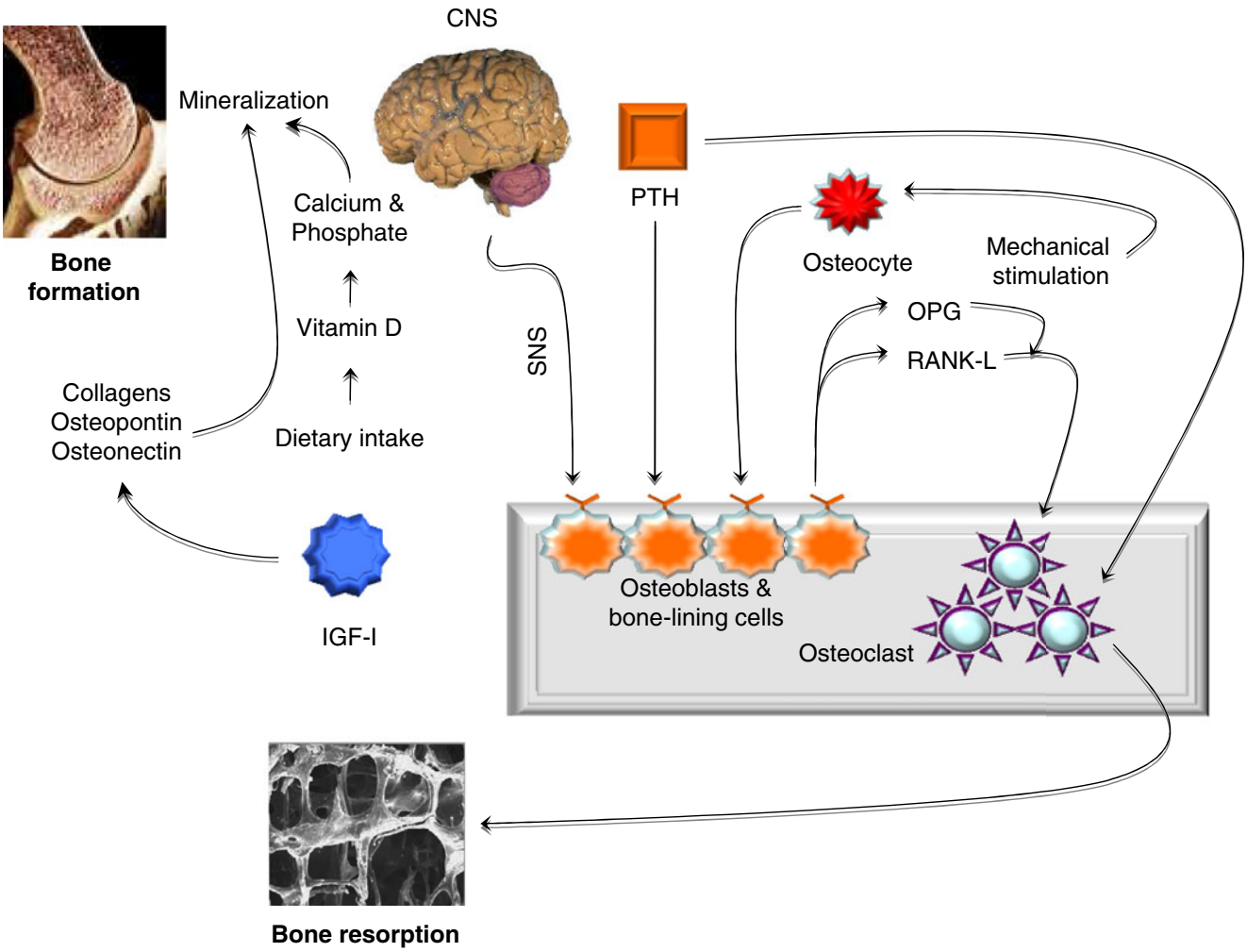

Fig. 1 The bone remodeling process. Bone remodeling is a dynamic process in which old bone is removed and new bone is formed. It consists of two distinct stages—formation and resorption—that involves the activity of special cells termed osteoblasts and osteoclasts. **a** Mature mineralizing osteoblasts differentiate terminally into osteocytes. Osteocytes communicate with each other but also communicate with osteocytes through gap junctions and respond to changes in fluid flow arising from stress or mechanical stimulation. Important extrinsic anabolic signals, such as PTH, IGF-I, and mechanotransduction, stimulate bone formation whereas hypothalamic leptinergic signals transmitted through adrenergic nerves inhibit bone formation. Dietary intake of vitamin D influences calcium and phosphate metabolism and impacts the bone mineralization and formation. Bone formation is completed when the bone surface is restored and covered by a layer of protective bone cells called bone-lining cells. **b** Bone resorption. In this phase, osteoclasts act on the trabecular bone surface to erode the mineral and matrix. Osteoclasts are terminally differentiated bone-absorbing cells. Bone resorption is accomplished by a series of tightly orchestrated molecular and biochemical changes that eventually results in the creation of small cavities on the surface of the trabecular bone. The main switch for osteoclastic bone resorption is the RANK-L that is released by activated osteoblasts. Its action on the RANK receptor is regulated by OPG, which is also derived from osteoblasts. *CNS* central nervous system; *IGF-I* insulin-like growth-hormone I; *OPG* osteoprotegerin; *PTH* parathyroid hormone; *RANK-L* receptor activator for NF-κβ-ligand, *SNS* sympathetic nervous system

inactivity diminishes mechanical loads by influencing linear growth and muscle mass and may alter the functional muscle-bone set point [31]. The risk for hip fractures decreases as physical activity increases. Non-randomized trials have shown that exercise protects against bone loss [32].

Pro-inflammatory cytokines stimulate RANKL expression in osteoblasts. Enhanced production of RANKL promotes osteoclast differentiation and stimulates bone resorption activity of osteoclasts. TNF-α and IL-1 synergize with RANKL and stimulate bone resorption by osteoclasts [33, 34]. Rate of bone resorption is in equilibrium with the rate of bone formation during bone remodeling. Newly formed bone completely replaces the bone lost in the resorption phase. Inflammation may uncouple this tightly regulated bone remodeling cycle,

resulting in negative bone balance. Pro-inflammatory cytokines such as IL-6 and IL-1β promote the expression of calcium-sensing receptor and result in decreased circulating PTH and vitamin D levels [35, 36]. Anti-TNF-α therapy is very effective in treating patients with inflammatory disorders. This treatment improves the underlying condition but also appears to have an independent beneficial effect on bone, probably via the inhibition of osteoclastogenesis [1].

An additional mechanism by which inflammation uncouples bone remodeling cycle is through alternation of glucocorticoid signaling [1]. Glucocorticoids suppress inflammation and help to resolve underlying illness. However, glucocorticoid treatment has been associated with osteopenia in chronic inflammatory disease [37]. Glucocorticoids reduce osteoblast protein synthesis [38]. While glucocorticoids at physiological doses are essential for normal osteoblast differentiation [39], glucocorticoids at high doses diminish the number of osteoblasts by promoting apoptosis [40]. Glucocorticoids can also cause muscle wasting [41]. Glucocorticoid-induced myopathy may contribute to bone deficits via the functional muscle-bone unit. Recent studies suggest divergent effects of glucocorticoids on bone metabolism. There is currently debate in the pediatric bone field regarding the skeletal effects of glucocorticoids. Results suggested that children with oral corticosteroid treatment were at a greater risk of bone fracture, likely due to decreased bone formation [37]. Modest deficits in bone mineral content (BMC) in the lumbar spine but greater whole body BMC and femoral shaft dimensions were observed in pediatric patients with steroid-sensitive nephrotic syndrome compared with controls [42]. In a follow-up study, glucocorticoids in childhood nephrotic syndrome were associated with low trabecular bone mineral density (BMD) but high cortical BMD and increased cortical dimensions were related to increased muscle mass [43].

Bone mass regulation in rheumatic diseases

Rheumatoid arthritis, juvenile idiopathic arthritis, the seronegative spondyloarthropathies including psoriatic arthritis, and systemic lupus erythematosus are all examples of rheumatic diseases in which inflammation is associated with skeletal pathology [44]. Although some of the mechanisms of skeletal remodeling are shared among these diseases, each disease has a unique impact on articular bone or on the axial or appendicular skeleton [45, 46]. Studies in human disease and in animal models of arthritis have identified the osteoclast as the predominant cell type mediating bone loss in arthritis [44, 47]. Many of the cytokines and growth factors implicated in rheumatic diseases have been demonstrated to impact osteoclast differentiation and function either directly, by acting on cells of the osteoclast-lineage, or indirectly, by acting on other cell types to modulate expression of the key molecules such as RANKL and its inhibitor OPG [48].

Reduced BMD and bone strength occurs in pediatric patients with rheumatoid arthritis [20, 49]. The hallmark of rheumatoid arthritis is inflammation of the synovium. The synovium becomes hyperplastic and inflamed, which is driven by innate and adaptive immune responses and subsequently invades the articular cartilage, causing bone erosions [50, 51]. Bone loss in the inflamed joint is also due to the uncoupling of bone remodeling. Pro-inflammatory cytokines released by activated immune cells in the inflamed joints promote osteoclast activity and bone erosion [1, 2, 51]. IL-17 recruits neutrophils to the inflamed joint and activates osteoclast differentiation by increasing the expression of RANK/RANKL in synoviocytes [52]. IL-17 also decreases the expression of OPG in osteoblastic cells, which promotes osteoclastogenesis and induces local bone erosion [53]. Other pivotal pro-inflammatory cytokines present in the arthritic joint include TNF-α, IL-6, IL-1, and IL-10 [54]. An additional pathway in which rheumatoid arthritis affects bone mass is through paracrine activity of 11β-hydroxysteroid dehydrogenases (11β-HSDs), potentially a major mechanism by which osteoblasts and osteoclasts are uncoupled [1]. Activities of 11β-HSDs were stimulated by pro-inflammatory cytokines, specifically IL-1 and TNF-α, suggesting that these factors might contribute to inflammation-mediated bone loss [55–58].

Juvenile idiopathic arthritis is the most common pediatric rheumatic disease [59] and affects joints in any part of the body. In this disease, the synovium and inflammation process can spread to surrounding tissues, eventually damaging cartilage and bone. Other areas of the body, especially the eyes, may also be affected by the inflammation. Without treatment, juvenile idiopathic arthritis can interfere with a child's normal growth and development. Burnham et al. have evaluated the bone density, structure, and strength in 101 pediatrics patients with juvenile idiopathic arthritis as compared to 830 healthy control subjects. Significant reduction in trabecular volumetric BMD and reduced bone strength was observed among those patients [20, 49, 60, 61]. Children with juvenile idiopathic arthritis are at risk for deleterious alternations in cortical bone strength and trabecular bone density, placing them at greater risk of bone fracture. The pronounced bone deficits are greater than would be expected for their reductions in muscle cross-sectional area. Thus, bone alternations in juvenile idiopathic arthritis could represent a mixed defect of bone development and low muscle forces [49].

Bone mass regulation in inflammatory bowel disease

Low BMD is common in patients with inflammatory bowel disease [62, 63]. Poor nutrition, physical inactivity, exposure to glucocorticoids, decreased muscle mass, inflammatory cells, and cytokines all contribute to low BMD in inflammatory bowel disease. Nutritional supplementations have reversed growth impairment in patients with inflammatory bowel disorder and benefited bone mineralization [51]. Lean tissue mass correlated positively with lumbar spine and total body BMD. Increased lean tissue mass may be related to improved physical activity which in turn, may increase BMD in children with inflammatory bowel disease [51, 64–67]. Vitamin D deficiency may play a role in the pathological process of bone loss in inflammatory bowel disease. Low serum 25-hydroxyvitamin D levels have been reported in patients with chronic inflammatory bowel disease [68]. Soluble factors released by the inflamed intestine may impair bone formation [69]. Activated lymphocytes are present in the inflamed intestinal mucosa in inflammatory bowel disease. Activated lymphocytes and their secreted cytokines affect bone cell function. TNF-α and IFN-γ inhibit osteoblast formation and function, and TNF-α stimulates osteoclast formation via RANKL. Neutralization of TNF-α in patients with inflammatory bowel disease is associated with a rise in bone formation biomarkers and improved BMD [65, 70].

Sylvester et al. reported inconsistent findings with regard to biomarkers of bone resorption in pediatric patients with Crohn's disease. Urinary N-telopeptides of collagen levels were decreased while urine deoxypyridinoline to creatinine ratios were not [71]. Possible reasons for the lack of elevated resorption markers in Crohn's disease in the Sylvester's study may be contributed to study design and analytic approach. Recent studies suggest that biomarkers of bone metabolism vary significantly with many confounding factors such as age, sex, and Tanner stage with a peak during the pubertal growth spurt followed by a rapid decline to adult levels [72–76]. After adjustment for these effects, Tuchman et al. reported that Crohn's disease was associated with lower biomarkers of bone formation and greater bone resorption [66]. Beneficial anti-inflammatory effects of glucocorticoids may offset some of its negative effects on bone. Dubner et al. carried out an elegant study in children with new-onset of Crohn's disease. Their protocol was rigorously designed to adjust for numerous variables that may affect bone density, structure, or strength in the participants. In this study, glucocorticoid treatment was directly correlated with increased cortical BMD Z-score after 6 months, and the absence thereof with declines in cortical BMD in the subsequent 6 months [64]. The authors speculated that glucocorticoids may lead to a reduction in bone turnover, possibly causing reduced intracortical porosity, greater secondary mineralization, and higher cortical BMD. 11β-HSD1 is induced by inflammatory cytokines [1, 77]. Upregulation of 11β-HSD1 is documented in colonic mucosa in experimental colitis [78] and in patients with inflammatory bowel disease [79]. Un-regulation of 11β-HSD1 increases the sensitivity of the colon to therapeutic glucocorticoids [1, 80]. A high 11β-HSD1 activity in the inflamed colon may lead to more effective anti-inflammatory effects on the colon, enabling a lower level of glucocorticoids to be used. This could have a potential bone-sparing effect.

Bone mass regulation in chronic kidney disease

Reductions in BMD are common in patients with chronic kidney disease (CKD) and may increase susceptibility to low-trauma fracture [81, 82]. Multiple factors may attribute to decreased bone formation in chronic kidney disease (Fig. 2). A wide spectrum of skeletal manifestations may occur in CKD [83]. Renal osteodystrophy is important in CKD children because of the risk of long-term consequences such as growth retardation and bone deformalities [84, 85]. Growth failure is a significant problem in CKD [86]. Pediatric patients have unique problems because CKD profoundly interferes with bone growth and mineralization [87, 88]. Secondary hyperparathyroidism is associated with excessive bone resorption and high turnover bone disease whereas sub-optimal PTH levels may cause low turnover bone disease [89]. Recent findings suggest that inflammation negatively impacts bone mass in CKD. IL-6, the major mediator of the acute-phase inflammation, is elevated in CKD patients [90]. A number of factors such as hypertension, adiposity, insulin resistance, fluid overload, persistent infections, genetic variations of IL-6 gene, reduced renal function, and dialysis per se have been implicated in the pathogenesis of increased IL-6 levels in CKD [91, 92]. Increased circulatory levels of IL-6 may uncouple bone remodeling in end-stage renal disease (ESRD). IL-6 affects bone turnover independently of PTH. An inverse correlation between serum IL-6 and the bone turnover markers osteocalcin and β-isomerized C-terminal cross-linked peptide of collagen type I was documented in hemodialysis patients [93]. Indeed, calcitriol treatment affects bone remodeling by influencing the levels of plasma IL-6, beyond its suppressive effect on PTH [94]. IL-6, synthesized by osteoblasts in response to PTH, stimulates osteoclastogenesis and bone resorption in vitro, and has been implicated in the pathogenesis of bone loss in several inflammatory conditions. Increased serum IL-6 levels were associated with elevated bone resorption rate in uremic patients with renal osteodystrophy [95]. IL-6, released from human osteoblastic cells in the uremic milieu, has been implicated in the

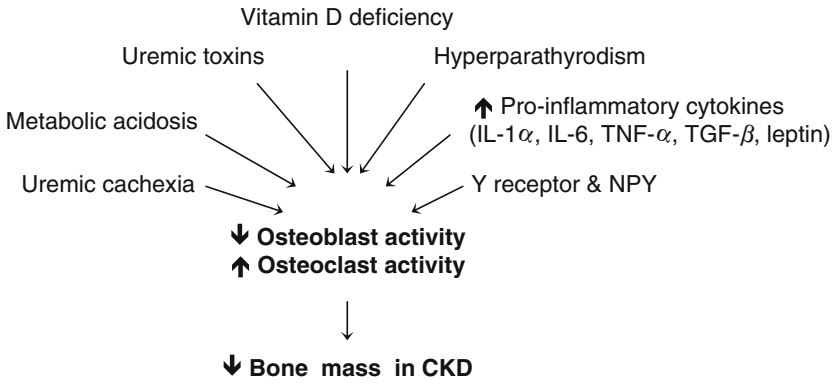

Fig. 2 Multiple factors may contribute to decreased bone formation in chronic kidney disease

deranged bone turnover of uremic patients [96]. Osteoblastic IL-6 secretion was negatively associated with osteoblastic cell growth in dialysis patients with low bone turnover [97]. Increased expression of IL-1α, IL-6, TNF-α, and TGF-β has been demonstrated in bone marrow in ESRD patients. IL-6 and TGF-β were also detected in osteoblasts and osteocytes. The extent of cytokine deposition corresponded to the severity of renal osteodystrophy [98], suggesting an important role of cytokines in the pathogenesis of renal osteodystrophy. IL-6 exerts its action by binding to its receptor (IL6R) and transduces subsequent signaling within cells. In vitro as well as in vivo data point to IL-6 as an autocrine/paracrine factor in bone osteoclasts. Increased mRNA expression of IL-6 and IL6R was found in osteoclasts and bone marrow cells in iliac crest bone biopsies from ESRD patients [99]. Thus, chronic inflammation in CKD has a negative impact on bone remodeling. Pro-inflammatory cytokines may contribute to the pathogenesis of renal osteodystrophy.

Neuropeptides and bone mass regulation in chronic kidney disease

Cytokines signal through CNS and influence bone remodeling [100, 101]. Central to this hypothesis is the discovery that leptin is an important regulator of bone mass. The characterization of the sympathetic nervous system as a regulator of bone remodeling has led to several clinical studies demonstrating a substantial protective effect of ß-blockers, particularly ß1-blockers, on fracture risk [102]. Studies in several model organisms have reinforced the role of the CNS in the regulation of bone remodeling by the identification of several additional genes such as melanocortin 4 receptor (MC4R), neuropeptide Y (NPY), Y2 receptor, cannabinoid receptor CB1 (Cnbr1), and the genes of the circadian clock [101]. These genes have several common features, including high levels of expression in the hypothalamus and the ability to regulate other major physiological functions in addition to bone remodeling including energy homeostasis, body weight, and reproduction.

Leptin plays a key role in skeletal physiology. Leptin-deficient (ob/ob), leptin receptor-deficient (db/db) and lipodystrophic mice, all of which exhibit decreased leptin signaling, have the same high bone mass phenotype [103]. Leptin is cleared from the circulation by the kidney [104, 105]. In CKD patients, serum levels of leptin were significantly increased [105, 106]. Elevated leptin level is a potent inhibitor of bone formation [100, 103]. High serum leptin levels are reported in several disorders, typically associated with osteopenia, such as liver cirrhosis, type 2 diabetes, and ESRD [107]. An inverse correlation between serum leptin levels and histomorphometric indicators of bone turnover has been demonstrated in renal bone disease. Serum leptin inversely correlated with PTH, bone formation rate, and mineral deposition rate in chronic dialysis patients. A complementary analysis in the same study in male dialysis patients revealed that the risk for low turnover bone disease increases with serum leptin concentrations. Adynamic bone disease is five times higher in patients with high serum leptin (third tertile) than those with relatively low serum leptin (first tertile) [108].

We demonstrated that elevated leptin levels may be an important cause of uremia-associated cachexia via signaling through the hypothalamic melanocortin system [109]. Leptin signaling is an important regulator of bone metabolism. Leptin acts centrally through the hypothalamic melanocortin receptors to affect appetite, metabolic rate, and bone mass [100]. Patients with loss-of-function mutations of melanocortin-4 receptor (MC4R) have markedly increased total body BMC and increased BMD [110], suggesting that leptin may regulate bone mass by increasing melanocortin receptor mediated signaling. We evaluated the role of leptin and melanocortin signaling on bone mass and bone strength in a mouse model of uremia. We showed that uremia induced in c57Bl/6J mice by subtotal nephrectomy resulted in elevated BUN, creatinine, and circulating leptin levels compared to pair-fed sham-operated mice. Whole-body and femoral BMC/BMD in nephrectomized c57Bl/6J mice were

significantly lower than those in sham-operated mice. Femoral bone volume was markedly reduced in nephrectomized c57Bl/6J mice and this reduction was due to decreased cortical bone volume rather than cancellous bone volume. Cortical bone provides strength by being highly resistant to bending and torsion while cancellous bone has a vast surface area created by an interconnecting trabecular meshwork. The reduced femoral bone BMC/BMD and femoral cortical bone volume contributed to the observed reduction of femoral load to failure (a measure of bone strength and fracture risk) in nephrectomized c57Bl/6J mice. Agouti-related peptide (AgRP), a melanocortin receptor reverse agonist, was associated with increase in cortical bone volume but no change in cancellous bone volume as well as improved cortical bone strength [111]. These results in mice are consistent with clinical data from patients with CKD on dialysis in which decreases in cortical but not cancellous bone correlated with fracture risk. Hence, our results suggest that aberrant leptin signaling through melanocortin receptors may play an important role in the decreased bone mass and strength associated with CKD.

Neuropeptide Y (NPY) is a target of leptin signaling in the hypothalamus and functions through its receptors. Immunoreactivity of NPY is found in nerve fibers distributed throughout bone [112], strongly suggesting a role of NPY in the regulation of bone metabolism. NPY Y2-deficient mice display an increase in trabecular bone mass that can be reproduced by hypothalamus-specific deletion of Y2 gene [113], indicating that Y2 signaling in the hypothalamus inhibits bone formation. Recent studies indicate that signaling of Y2 receptor regulates, via a hypothalamic relay, the bone remodeling process in both femoral trabecular and cortical bone compartments [114]. Circulating levels of NPY are elevated in ESRD patients [115]. Whether the role of Y receptor and NPY signaling in bone metabolism is conserved from mouse to humans is unknown.

Conclusions

Chronic inflammatory diseases are characterized by systemic and local bone loss. The clinical picture is a composite of inflammatory lesions and structural damage, demonstrating the tight interaction between the immune and the skeletal system. Growing knowledge of the molecular mechanisms involved in the uncoupled bone metabolism has revealed potential targets for therapeutic interventions.

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