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Review Article

The influence of uremic toxins on low bone turnover disease in chronic kidney disease

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Abstract

Uremic toxins play a crucial role in the development of low bone turnover disease in chronic kidney disease (CKD) through the induction of oxidative stress. This oxidative stress disrupts the delicate balance between bone formation and resorption, resulting in a decline in both bone quantity and quality. Reactive oxygen species (ROS) activate nuclear factor kappa-B and mitogen-activated protein kinase signaling pathways, promoting osteoclastogenesis. Conversely, ROS hinder osteoblast differentiation by facilitating the binding of Forkhead box O proteins (FoxOs) to β-catenin, triggering apoptosis through FoxOs-activating kinase phosphorylation. This results in increased osteoblastic receptor activator of nuclear factor kappa-B ligand (RANKL) expression and decreased nuclear factor erythroid 2-related factor 2 levels, compromising antioxidant defenses against oxidative damage. As CKD progresses, the accumulation of protein-bound uremic toxins such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS) intensifies oxidative stress, primarily affecting osteoblasts. IS and PCS directly inhibit osteoblast viability, induce apoptosis, decrease alkaline phosphatase activity, and impair collagen 1 and osteonectin, impeding bone formation. They also reduce cyclic adenosine 3',5'-monophosphate (cAMP) production and lower parathyroid hormone (PTH) receptor expression in osteoblasts, resulting in PTH hyporesponsiveness. In summary, excessive production of ROS by uremic toxins not only reduces the number and function of osteoblasts but also induces PTH hyporesponsiveness, contributing to the initiation and progression of low bone turnover disease in CKD.

Keywords: *Chronic kidney disease, Low bone turnover disease, Oxidative stress, Uremic toxins*

Low bone turnover disease in chronic kidney disease

During the early stages of chronic kidney disease (CKD) stage 1 or 2, there is an increase in Wingless (Wnt) signaling inhibitors such as dickkopf-1 and sclerostin, which are responsible for suppressing the viability of osteoblast cells [1]. Additionally, the accumulation of protein-bound uremic toxins such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS) further worsens the viability of both osteoblasts and osteoclasts, affecting their bone formation and resorption activity [2]. In this stage, bone quality is compromised while bone mass remains relatively normal, a condition referred to as uremic osteoporosis [3].

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As CKD progresses beyond stage 3, it can cause mineral and hormonal imbalances, along with Vitamin D deficiencies, leading to CKD patients experiencing either elevated or reduced parathyroid hormone (PTH) levels [4]. When PTH levels are high, they stimulate osteoblast activity and simultaneously increase the osteoclastic nuclear factor kappa-B ligand (receptor activator of nuclear factor kappa-B ligand [RANKL]) gene, resulting in excessive bone resorption that exceeds bone formation, leading to a loss of bone quantity. In addition, high PTH levels negatively affect bone quality [5].

Conversely, low PTH levels, which can occur due to over-suppression of hyperparathyroidism by PTH-lowering medicine or after parathyroidectomy, fail to stimulate osteoblast activity and, consequently, osteoclast activity [6,7]. This is due to the RANKL/osteoprotegerin (OPG) system's coupling mechanism. Despite increased osteoclast activity caused by CKD-related oxidative stress, low PTH levels lead to reduced bone formation and resorption, ultimately resulting in bone loss.

Uremic toxins play a significant role in increasing oxidative stress levels among individuals with CKD. These toxins possess prooxidant properties that actively stimulate the production of harmful reactive oxygen species (ROS) in the body [7,8]. This heightened oxidative stress has detrimental effects on bone health. The mechanisms by which uremic toxins induce oxidative stress in bone cells are complex, but it is evident that these toxins interact with various signaling pathways within bone cells, triggering ROS production while hindering antioxidant defense mechanisms [9]. Consequently, an excessive accumulation of ROS ensues, leading to damage and dysfunction in bone cells. This compromises their capacity for proper differentiation and optimal function. This article aims to provide a comprehensive exploration of the prooxidant properties of uremic toxins specifically in bone cells. By shedding light on the disruptions caused by these toxins in the normal bone turnover process, we can gain a better understanding of their implications in the development of low bone turnover disease.

Impact of oxidative stress on bone components

Osteoclasts

Maintaining a delicate balance in the physiological redox state is crucial for optimal osteoclast function. The differentiation of bone marrow monocyte-macrophage lineage (BMM) cells into osteoclasts relies on the presence of RANKL [10]. When BMM cells are stimulated by RANKL, it initiates a signaling cascade involving tumor necrosis factor receptor-associated factors 6 (TRAF6), Rac Family Small GTPase 1, and nicotinamide adenine dinucleotide phosphate oxidase 1, leading to a transient increase in physiological ROS production [10]. Under normal conditions, low levels of ROS serve as vital secondary messengers in the RANKL-mediated signaling pathway, promoting osteoclast differentiation. In response to elevated ROS production, osteoblasts in the surrounding environment activate antioxidant systems to counterbalance ROS effects [11]. Thus, maintaining an appropriate balance in the physiological redox state is crucial for optimal osteoclast functionality.

Disruption of this delicate balance has significant implications for bone health. An imbalanced redox status, resulting in increased ROS levels, has a dual effect on bone metabolism. First, it contributes to the stimulation of osteoclastogenesis, the process of osteoclast formation. Second, it reduces osteoblast activity, which is responsible for bone formation [12,13]. Elevated ROS production plays a crucial role in enhancing the expression of nuclear factor kappa-B (NF-κB), a protein that stimulates downstream signals involved in osteoclast differentiation, such as c-Fos and nuclear factor of activated T cells 1 (NFATc1). These signals promote osteoclastogenesis, leading to the formation of mature osteoclasts [14]. In addition, ROS production mediated by RANKL activates mitogen-activated protein kinase (MAPK) signaling pathways, including extracellular signal-regulated kinase (ERK), Jun N-terminal kinase (JNK), and p38 MAPK. These pathways further promote osteoclast differentiation and regulate gene expression during the process [15]. ROS also induces the expression of TRAF6, a key activator of NF-κB, intensifying molecular reactions associated with osteoclastogenesis and sustaining osteoclast differentiation [16,17].

Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor activated by oxidative stress, plays a crucial role in protecting against the harmful effects of excessive-free radicals [18]. Nrf2 activation leads to the upregulation of specific genes involved in antioxidant and detoxification processes, mediated by antioxidant response elements (AREs) [19]. In the context of osteoclastogenesis, Nrf2 has a dual role. First, it promotes the formation and activity of osteoclasts by inhibiting osteoblasts' secretion of OPG. OPG is a protein that normally prevents excessive bone resorption by binding to RANKL and inhibiting its interaction with RANK on osteoclast precursors [20]. By reducing OPG secretion, Nrf2 indirectly promotes osteoclastogenesis [21]. Second, Nrf2 provides protective effects during osteoclastogenesis by reducing ROS through the inhibition of ERK and p38 signal activation and the suppression of inflammation production, utilizing its antioxidant and anti-inflammatory functions. By increasing the expression of antioxidant enzymes, such as heme oxygenase-1 and NAD (P) H quinone oxidoreductase 1, Nrf2 helps maintain a balanced redox state, limiting excessive ROS generation and suppressing the inflammatory response associated with osteoclastogenesis [21].

Emerging research highlights the significance of Nrf2 in maintaining bone mass and preserving bone's structural integrity, particularly in the face of oxidative stressors [22-24]. Despite its dual function in regulating osteoclastogenesis, Nrf2 is a key player in safeguarding optimal bone health and preventing detrimental imbalances in osteoclast activity. Nrf2's involvement in osteoclastogenesis entails two important aspects [21]. Firstly, it promotes the formation and activity of osteoclasts, the cells responsible for bone resorption. However, this pro-osteoclastogenic effect is accompanied by

a crucial role in mitigating oxidative stress and inflammation within the skeletal system. By increasing antioxidant enzyme expression and reducing inflammation, Nrf2 helps maintain a delicate balance necessary for preserving bone health [22-24]. Consequently, in individuals with CKD, when Nrf2 levels decrease, it results in more oxidative stress within osteoclasts, exacerbating the formation of osteoclasts [25,26].

In summary, Figure 1 demonstrates that oxidative stress triggers osteoclast differentiation through the activation of NF-κB and MAPK signaling pathways. However, in the context of CKD, compromised Nrf2 antioxidant capacity disrupts this delicate balance, leading to increased oxidative stress and inflammation, promoting osteoclast formation, and heightened osteoclast activity.

Osteoblasts

In contrast to their role as signaling mediators in osteoclasts, ROS have a detrimental impact on osteoblast differentiation, proliferation, and survival [27]. Studies on the differentiation of mouse calvarial cells into osteoblasts have shown that the use of N-acetyl cysteine, a compound that scavenges ROS, effectively enhances alkaline phosphatase activity, mRNA expression of genes associated with osteoblast differentiation, and the formation of mineralized nodules. This indicates that the presence of ROS negatively influences osteoblast differentiation [28,29].

Nrf2, similar to redox-sensitive transcription factors in osteoclasts, acts as a protective mechanism for osteoblasts against oxidative stress-induced damage. Nrf2 levels and downstream antioxidant enzyme activity play a critical role in maintaining a balanced cellular redox state within osteoblasts, counteracting the harmful effects of oxidative stress during osteoblast differentiation [23]. Chemical compounds such as melatonin and luteolin have been found to rescue osteoblasts from oxidative stress-induced cytotoxicity by activating the Nrf2/ARE signaling pathway [30,31]. Conversely, deletion of Nrf2 in osteoblasts results in significantly increased ROS production due to lower glutathione levels. Moderate hyperactivation of Nrf2, on the other hand, upregulates Wnt 5a and alkaline phosphatase expression in primary cultured osteoblast cells [32]. Studies have also demonstrated that Nrf2 knockout mice calvarial osteoblasts exhibit reduced numbers of osteoblasts and decreased matrix mineralization [33]. In summary, by maintaining an optimal balance of antioxidants, Nrf2 actively contributes to protecting osteoblasts from oxidative stress-induced harm. Its presence and activity are crucial for mitigating the detrimental effects of oxidative stress during osteoblast differentiation, ensuring the integrity and functionality of osteoblasts in bone health.

The Forkhead box O proteins (FoxOs) are a group of redox-sensitive transcription factors that play a significant

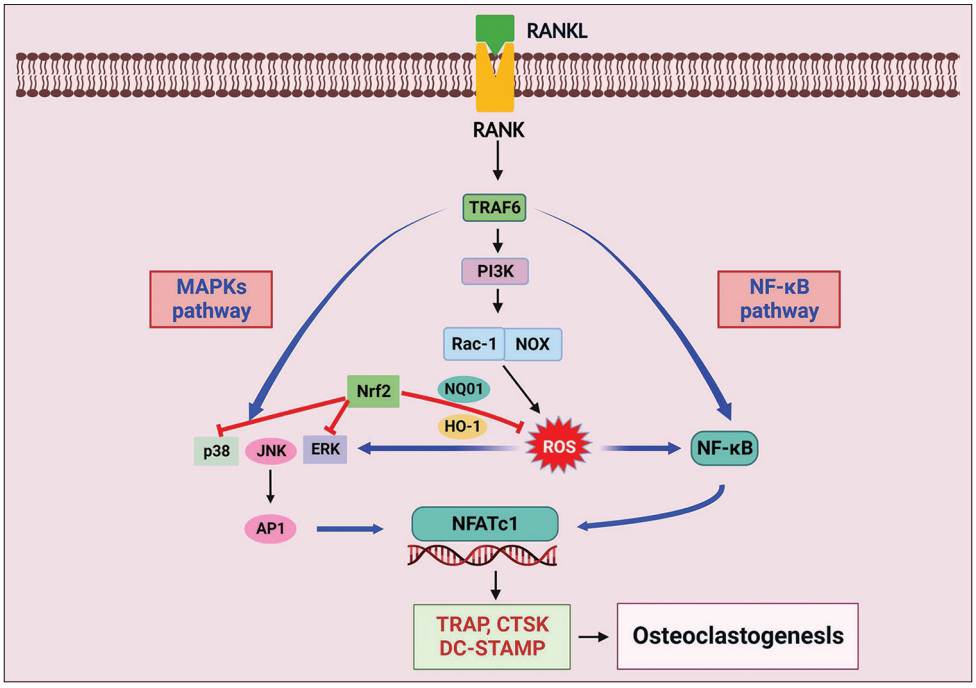

Figure 1: Chronic kidney disease (CKD) is associated with oxidative stress, which plays a crucial role in triggering osteoclast differentiation. Within the bone marrow, Monocyte-macrophage lineage cells can differentiate into osteoclasts when RANK interacts with RANKL. This process involves RANKL initiating a signaling cascade that includes TRAF6, Rac1, and NOX1. The activation of NOX1 leads to the production of ROS, which act as secondary messengers to promote osteoclast differentiation. The increased ROS production also activates two signaling pathways, NF-κB and MAPK, both of which potentiate osteoclast differentiation and regulate the expression of genes essential for osteoclast function, including TRAP, CTSK, and DC-STAMP. In CKD, compromised Nrf2 function fails to inhibit the ROS-mediated activation of MAPK (ERK and p38) and the expression of antioxidant enzymes (HO-1 and NQO1). Consequently, this leads to an accumulation of oxidative stress, exacerbating osteoclast differentiation and bone resorption. CTSK: cathepsin K; DC-STAMP: Dendritic cell-specific transmembrane protein; ERK: Extracellular signal-regulated kinase; HO-1: Heme oxygenase-1; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa-B; NOX1: nicotinamide adenine dinucleotide phosphate oxidase 1; NOQ1: NAD (p) H quinone oxidoreductase 1; Nrf2: Nuclear factor erythroid 2-related factor 2; Rac1: Rac family small GTPase 1; RANK: receptor activator of nuclear factor kappa-B; RANKL: RANK ligand; ROS: reactive oxygen species; TRAF6: Tumor necrosis factor receptor-associated factors 6; TRAP: tartrate-resistant acid phosphatase; PI3K: Phosphatidylinositol-3-kinase; JNK: Jun N-terminal kinase

role in various cellular processes, including proliferation, differentiation, apoptosis, and stress resistance [34]. These proteins act as essential defense mechanisms against oxidative stress, crucial for cellular protection. One of their primary functions is to safeguard cells from the harmful effects of ROS by upregulating antioxidant enzymes such as catalase, manganese superoxide dismutase, and glutathione peroxidase-1 [35,36]. By increasing antioxidant enzyme production, FoxOs help mitigate the detrimental impact of ROS on cellular components, maintaining cellular homeostasis and preventing oxidative damage [37]. In the context of CKD, disruptions in FoxOs' activity and associated antioxidant enzymes contribute to exacerbated oxidative burden, significantly affecting bone loss in CKD [38,39]. Compromised FoxOs function and decreased antioxidant enzyme expression worsen the imbalance between ROS production and cellular antioxidant defenses, resulting in increased oxidative damage in bone cells.

FoxOs proteins are typically located in the nucleus of quiescent cells, regulating gene transcription. On stimulation by growth factors, FoxOs proteins undergo phosphorylation and translocate from the nucleus to the cytosol, facilitated by protein interactions such as with 14-3-3 [40]. In the cytosol, FoxOs proteins can be degraded through the ubiquitin-proteasome pathway. To enhance their activity, FoxOs proteins require the assistance of cAMP-response element-binding protein and its paralog p300 (CBP/p300), possessing histone acetyltransferase (HAT) activity, which promotes chromatin accessibility for FoxOs binding to target genes [41]. Another critical regulator of FoxOs proteins is Sirtuin-1 (SIRT1), which deacetylates specific lysine residues in FoxOs proteins, inhibiting their acetylation [42]. This deacetylation modulates FoxOs proteins' activity and function. In summary, FoxOs proteins exhibit dynamic behavior within cells, primarily located in the nucleus but capable of translocating to the cytosol upon stimulation. Their translocation is facilitated by protein interactions, such as with 14-3-3. In the cytosol, FoxOs proteins can be degraded but can be enhanced through interactions with CBP/p300, promoting chromatin accessibility. Additionally, SIRT1 plays a crucial role in FoxOs proteins' deacetylation, impacting their function [43].

The insulin/insulin-like growth factor-1/phosphatidylinositol-3-kinase/Akt signaling pathway acts as a negative regulator, inhibiting the transcriptional activity of FoxOs transcription factors [44]. Phosphorylation under this pathway leads to FoxOs' exclusion from the nucleus. Conversely, oxidative stress affects FoxOs' subcellular localization differently. Signals generated by oxidative stress activate specific kinases known as FoxOs-activating kinases, including JNK, AMPK, and mammalian sterile 20-like kinase-1 [45]. Activation of these kinases results in the nuclear translocation of FoxOs, initiating transcriptional activation of genes involved in various cellular processes, including ROS detoxification, cell-cycle arrest, DNA repair, and cellular apoptosis. Figure 2a illustrates FoxOs' involvement in these cellular processes, highlighting their role in response to oxidative stress [46,47].

FoxOs are highly expressed in bone cells and play a critical role as master signaling integrators in various pathological processes associated with oxidative stress. Conditional removal of FoxO1, FoxO3, and FoxO4 in Mx1-Cre+ mice led to increased oxidative stress levels in calvarial cell-derived cells. This alteration was accompanied by a decrease in the number of osteoblasts, reduced bone formation rate, and decreased bone volume in both spongy and compact regions [48].

β-catenin is known for promoting mesenchymal stem cell commitment to osteoblast differentiation by interacting with the T-cell factor/lymphoid enhancer binding factor (Tcf/Lef) complex [49]. In addition, β-catenin acts as a co-activator for FoxOs transcription factors. Under oxidative stress conditions, FoxOs' binding to β-catenin is facilitated, activating FoxOs' transcriptional activity. Consequently, the limited pool of transcriptional resources is diverted from the Tcf/Lef complex toward FoxOs. This diversion affects osteoblast proliferation and differentiation, resulting in reduced rates of both processes [Figure 2b] [50,51].

Moreover, ROS upregulates the expression of RANKL in human MG63 osteoblast cells, promoting osteoclastogenesis [52]. This process involves heat shock factor 2 (HSF2) binding to specific regions called heat shock factor-responsive elements (HSEs) within the human RANKL gene promoter [Figure 2c]. HSFs, produced in response to oxidative stress, act as molecular chaperones, aiding in the proper folding and refolding of proteins. In this context, HSF2 regulates RANKL expression by binding to HSEs and initiating RANKL gene transcription.

In summary, Figure 2 provides valuable insights into the detrimental effects of oxidative stress on osteoblast function. When exposed to oxidative stress, osteoblasts experience hindered differentiation and proliferation, compromising bone formation and remodeling. In addition, oxidative stress triggers osteoblast apoptosis, leading to reduced osteoblast numbers. Excessive activation of ROS-stimulated RANKL in osteoblast cells disrupts the balance between bone resorption and replenishment, ultimately resulting in excessive bone loss. The decreased expression of Nrf2, a transcription factor involved in antioxidant defense, further impairs osteoblasts' ability to combat oxidants, rendering them more susceptible to oxidative damage and exacerbating the negative effects of oxidative stress on bone health.

The induction of oxidative stress by uremic toxins and its effect on bone cells

Indoxyl sulfate

CKD is widely recognized for its association with elevated oxidative stress levels, a significant factor contributing to renal function deterioration. Among the culprits responsible for this oxidative stress is IS, a compound known for its prooxidant properties, which also exerts adverse effects on bone remodeling. Specifically, exposure to IS leads to a substantial increase in oxidative stress within osteoblasts, with the severity of oxidative stress being dose dependent. This heightened oxidative stress, in turn, negatively influences the viability of osteoblasts [53]. Furthermore, IS-induced

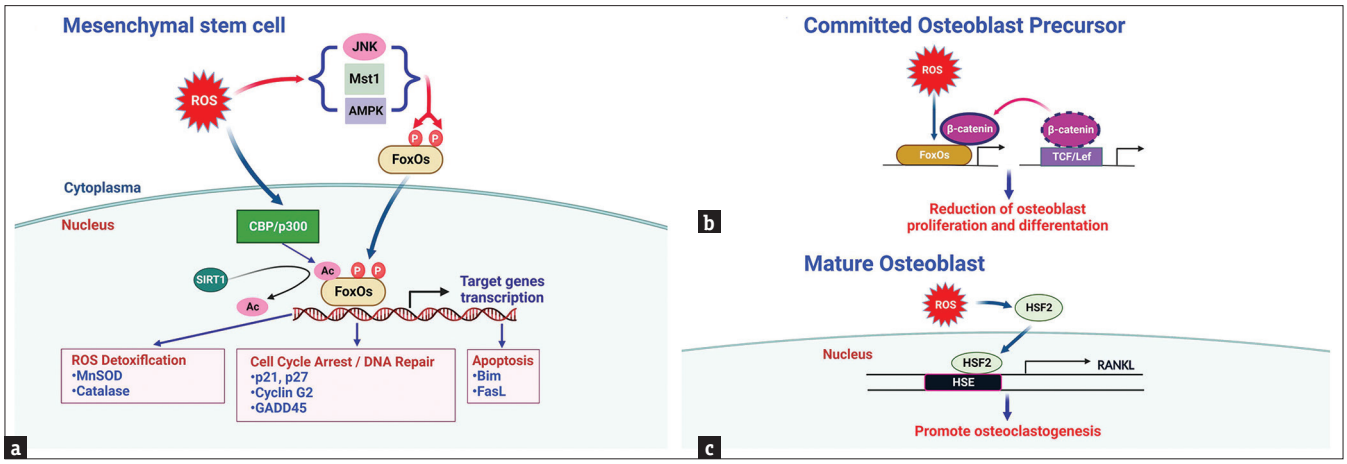

Figure 2: ROS play a significant role in negatively affecting osteoblast differentiation, proliferation, and survival. (a) ROS induce posttranslational modifications, such as phosphorylation and acetylation, activating FoxOs transcription factors. This activation leads to the upregulation of genes responsible for cellular detoxification, cell cycle arrest, DNA repair, and apoptosis of mesenchymal stem cells. Additionally, ROS enhance the phosphorylation of JNK, Mst1, and AMPK, as well as the acetylation of the enzyme complex CBP/p300, further contributing to these cellular responses. (b) ROS strengthen the binding between FoxOs and β-catenin, disrupting the binding of β-catenin to Tcf/Lef. As a result, committed osteoblast precursors experience negative impacts on both their proliferation and differentiation processes. (c) ROS promote the binding of HSF2 to HSEs within the human RANKL gene promoter, initiating RANKL gene transcription in mature osteoblasts. AMPK: adenosine monophosphate-activated protein kinase; CBP/p300: cAMP-response element-binding protein and its paralog p300; FoxOs: Forkhead box class O family member proteins; HSEs: heat shock factor-responsive elements; HSF2: heat shock factor 2; JNK: c-JUN N-terminal kinase; Mst1: Mammalian Sterile 20-like kinase 1; ROS: reactive oxygen species; Tcf/Lef: T-cell factor/lymphoid enhancer binding factor; Wnt: Wingless-related integration site; SIRT: Sirtuin-1; Mn-SOD: Manganese superoxide dismutase

oxidative stress triggers apoptosis in osteoblasts by enhancing the activity of caspase-3/7, enzymes involved in the programmed cell death process. Importantly, IS impedes the process of osteoblast differentiation by provoking oxidative stress, resulting in reduced alkaline phosphatase activity – an enzyme critical for bone formation. In addition, IS inhibits the production of collagen 1 and osteonectin, essential markers of bone formation [54].

In summary, the excessive production of ROS not only impacts cell viability and apoptosis but also disrupts the osteoblast differentiation process. This leads to a decrease in the number and functionality of osteoblasts, initiating and exacerbating osteoporotic processes. Moreover, the progressive decline in Nrf2 gene expression with advanced CKD stages, coupled with elevated IS levels, suggests that IS may contribute to reduced Nrf2 expression and increased oxidative burden in CKD, potentially causing oxidative damage to bone cells [55].

p-Cresyl sulfate

The introduction of PCS into osteoblasts significantly augments the production of ROS within these cells, underscoring the important role of PCS in this process. Consequently, the viability of osteoblasts is significantly compromised when exposed to PCS, indicating a detrimental effect on their overall survival. This adverse impact on osteoblast viability is further substantiated by the observation that PCS treatment leads to increased DNA fragmentation, indicative of induced apoptosis specifically in osteoblasts [56]. The cytotoxicity induced by PCS is closely linked to the activation of specific members of the MAPK family through phosphorylation, particularly the JNK and p38 MAPK pathways [57]. These phosphorylation events play a crucial role in mediating the deleterious effects of PCS on osteoblasts, exacerbating the adverse impact on both the viability and function of these cells [56]. In summary, the inhibitory effect of PCS on osteoblasts, characterized by reduced viability, increased apoptosis, and activation of MAPK pathways, plays a significant role in the progression of low bone turnover disease.

The induction of oxidative stress by uremic toxins and its effect on parathyroid hormone

PTH hyporesponsiveness refers to a condition characterized by a diminished ability to achieve the expected calcemic response to PTH. Activation of the PTH receptor 1 (PTH1R) in osteoblasts and osteocytes triggers various downstream pathways, including the adenylate cyclase/cAMP/protein kinase A pathway, which plays a crucial role in mediating the effects of PTH on bone remodeling [6,58]. The presence of IS has been shown to negatively affect the response of primary osteoblast cells to PTH. Studies reveal that IS can suppress cyclic adenosine 3',5'-monophosphate (cAMP) production and reduce the expression of PTH receptors, thereby diminishing the cellular response to PTH. In addition, when IS is transported into osteoblasts via the organic anion transporter-3, it triggers an increase in the production of intracellular free radicals. This oxidative stress induced by IS further downregulates the expression of the PTH1R, exacerbating the hyporesponsiveness to PTH [59]. Similarly, PCS also inhibits PTH-stimulated cAMP production and decreases PTH receptor mRNA expression [56]. Apart from uremic toxins, PTH hyporesponsiveness is influenced by various factors, including decreased levels of calcitriol [60], phosphate retention [61], abnormal metabolism of PTH and its fragments [62], and enhanced synthesis of inhibitors that target the Wnt signaling pathway [63]. The cumulative effect of these factors significantly contributes to the development of PTH hyporesponsiveness [64].

Pathological effect of uremic toxins on osteoclast in chronic kidney disease

Unlike the detrimental effects of IS and PCS on osteoblasts, IS exhibits a dual impact on osteoclasts. In a previous cellular study, we observed that the concentration and duration of IS exposure play a pivotal role in influencing the activity of the critical transcription factor NFATc1, which promotes osteoclast formation [65].

Short-term and low-dose exposure to IS enhances NFATc1 expression through the AhR nuclear translocator (ARNT), thereby supporting osteoclast differentiation, similar to the action of oxidative stress mentioned above. However, long-term and high-dose exposure to IS, as seen in CKD, transforms ARNT into an E3 ubiquitin ligase, leading to NFATc1 degradation and inhibition of osteoclast differentiation. Additionally, IS reduces the bone resorption surface area in a dose-dependent manner on bovine bone slices [66].

In summary, understanding how IS affects osteoclasts in the context of CKD is complex and intriguing. It becomes evident that in the progression of CKD, prolonged exposure to IS due to reduced kidney clearance becomes a significant factor in reducing osteoclast differentiation, proliferation, and bone-resorbing activity, contributing to the development of low bone turnover disease.

Potential mechanisms of uremic toxins associated with low bone turnover disease

In CKD, the excessive production of ROS exerts a dual effect on bone cells: promoting osteoclast activity while inhibiting osteoblast function. This imbalance disrupts the normal equilibrium of bone homeostasis, resulting in impaired bone tissue turnover. Furthermore, the accumulation of protein-bound uremic toxins exacerbates this imbalance due to their prooxidant properties and their influence on signaling pathways regulating the activity of both osteoblasts and osteoclasts. Table 1 provides evidence that these protein-bound uremic toxins primarily target osteoblasts, the cells responsible for bone formation. Consequently, they contribute to the further deterioration of low bone turnover, along with the reduced responsiveness to PTH. The combined effect of ROS and protein-bound uremic toxins plays a significant role in the progression of bone abnormalities in CKD.

Table 1: Potential mechanisms of uremic toxins associated with low bone turn over disease

IS
Inhibits osteoblast cell viability
Increases caspase - 3/7 activity, leading to osteoblast apoptosis
Decreases the activity of alkaline phosphatase, hindering bone formation
Impairs the production of collagen 1 and osteonectin, there by impeding bone formation
Decreasing Nrf2 expression renders bone cells more vulnerable to oxidative damage
Reducing cAMP production and lowering PTH1R expressions result in PTH hyporesponsiveness
PCS
Inhibits osteoblast cell viability by activating MAPK, especially JNK and p38
Induces osteoblast apoptosis
Reducing cAMP production and lowering PTH1R expressions result in PTH hyporesponsiveness

PCS: p-Cresyl sulfate, Nrf2: Nuclear factor erythroid 2, cAMP: Cyclic adenosine monophosphate, PTH: Parathyroid hormone, PTH1R: PTH receptor 1, MAPK: Mitogen-activated protein kinase, JNK: Jun N-terminal kinase, IS: Indoxyl sulfate

Conclusion

Oxidative stress plays a crucial role in the pathogenesis of bone fragility and fractures in individuals with CKD, affecting both the quantity and quality of bone. As CKD advances, the accumulation of protein-bound uremic toxins, such as IS and PCS, exacerbates oxidative stress levels. This heightened oxidative stress disrupts the delicate balance between bone formation and resorption. Moreover, these protein-bound uremic toxins possess prooxidant properties that further intensify the oxidative burden. As a result, the responsiveness of bone cells to PTH is reduced, leading to excessive suppression of bone formation. Consequently, a condition known as low bone turnover disease develops, characterized by a decreased rate of bone formation compared to bone resorption. The interplay between oxidative stress and the accumulation of protein-bound uremic toxins in CKD significantly contributes to impaired bone health. It underscores the importance of addressing oxidative stress and managing uremic toxins to mitigate the negative impact on bone metabolism and reduce the risk of bone fragility and fractures in individuals with CKD.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author (Dr. Chien-Lin Lu) on reasonable request.

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Conflicts of interest

Dr. Giou-Teng Yiang, an editorial board member at Tzu Chi Medical Journal, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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