ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2021 December 6; 9(34): 10392-10745

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents Thrice Monthly Volume 9 Number 34 December 6, 2021

World Journal of Clinical Cases

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World Journal of Clinical Cases

Thrice Monthly Volume 9 Number 34 December 6, 2021

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
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PUBLICATION DATE
December 6, 2021

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World J Clin Cases 2021 December 6; 9(34): 10616-10625

DOI: 10.12998/wjcc.v9.i34.10616

ISSN 2307-8960 (online)

SYSTEMATIC REVIEWS

Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease

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Author contributions: Zhang R initiated the project and gave constructive comments and suggestions for the manuscript; Kan C drafted the manuscript; Lu X provided assistance with the figures and tables; and all authors have read and approved the manuscript.

Conflict-of-interest statement: The authors declare that they have no competing interests to disclose.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

Specialty type: Urology and nephrology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C

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Abstract

BACKGROUND

Abnormal bone metabolism and renal anemia seriously affect the prognosis of patients with chronic kidney disease (CKD). Existing studies have mostly addressed the pathogenesis and treatment of bone metabolism abnormality and anemia in patients with CKD, but few have evaluated their mutual connection. Administration of exogenous erythropoietin to CKD patients with anemia used to be the mainstay of therapeutic approaches; however, with the availability of hypoxia-inducible factor (HIF) stabilizers such as roxadustat, more therapeutic choices for renal anemia are expected in the future. However, the effects posed by the hypoxic environment on both CKD complications remain incompletely understood.

AIM

To summarize the relationship between renal anemia and abnormal bone metabolism, and to discuss the influence of hypoxia on bone metabolism.

METHODS

CNKI and PubMed searches were performed using the key words "chronic kidney disease," "abnormal bone metabolism," "anemia," "hypoxia," and "HIF" to identify relevant articles published in multiple languages and fields. Reference lists from identified articles were reviewed to extract additional pertinent articles. Then we retrieved the Abstract and Introduction and searched the results from the literature, classified the extracted information, and summarized important information. Finally, we made our own conclusions.

RESULTS

There is a bidirectional relationship between renal anemia and abnormal bone metabolism. Abnormal vitamin D metabolism and hyperparathyroidism can

Grade D (Fair): 0
Grade E (Poor): 0

Received: May 7, 2021
Peer-review started: May 7, 2021
First decision: July 26, 2021
Revised: August 12, 2021
Accepted: October 25, 2021
Article in press: October 25, 2021
Published online: December 6, 2021

P-Reviewer: Vela D
S-Editor: Ma YJ
L-Editor: Wang TQ
P-Editor: Ma YJ

affect bone metabolism, blood cell production, and survival rates through multiple pathways. Anemia will further attenuate the normal bone growth. The hypoxic environment regulates bone morphogenetic protein, vascular endothelial growth factor, and neuropilin-1, and affects osteoblast/osteoclast maturation and differentiation through bone metabolic changes. Hypoxia preconditioning of mesenchymal stem cells (MSCs) can enhance their paracrine effects and promote fracture healing. Concurrently, hypoxia reduces the inhibitory effect on osteocyte differentiation by inhibiting the expression of fibroblast growth factor 23. Hypoxia potentially improves bone metabolism, but it still carries potential risks. The optimal concentration and duration of hypoxia remain unclear.

CONCLUSION
There is a bidirectional relationship between renal anemia and abnormal bone metabolism. Hypoxia may improve bone metabolism but the concentration and duration of hypoxia remain unclear and need further study.

Key Words: Chronic kidney disease; Abnormal bone metabolism; Anemia; Hypoxia; Hypoxia-inducible factor

Core Tip: Anemia and abnormal bone metabolism are complications in patients with chronic kidney disease (CKD), which seriously affect the prognosis of patients. This review summarizes the findings from recent studies on renal anemia and abnormal bone metabolism in patients with CKD. The bidirectional relationship between anemia and abnormal bone metabolism in patients with CKD is discussed. While studying the treatment of anemia with hypoxia-inducible factor (HIF), it was found that hypoxia can affect bone metabolism, but there is no consensus on the efficacy of HIF stabilizers in renal bone disease.

Citation: Kan C, Lu X, Zhang R. Effects of hypoxia on bone metabolism and anemia in patients with chronic kidney disease. *World J Clin Cases* 2021; 9(34): 10616-10625
URL: https://www.wjgnet.com/2307-8960/full/v9/i34/10616.htm
DOI: https://dx.doi.org/10.12998/wjcc.v9.i34.10616

INTRODUCTION

Chronic kidney disease (CKD) is defined according to the presence of kidney damage or an estimated glomerular filtration rate lower than 60 mL/min per 1.73 m^2 for 3 mo or longer[1]. In addition to sustained kidney damage, patients with CKD are also at increased risk of developing multiple complications including renal anemia, abnormal mineral and bone metabolism, dyslipidemia, and malnutrition. The pathophysiology of anemia in CKD includes many important factors such as the presence of comorbidities, erythropoietin (EPO) deficiency resulting from lower nephron mass, the resistance of bone marrow to EPO action due to uremic toxins, a reduced red cell life span, hepcidin metabolism dysfunction, absolute and functional deficiency of iron, and an increase in proinflammatory mediators[2]. Abnormal bone metabolism in patients with CKD stems from disorders involving calcium and phosphorus metabolism, vitamin D deficiency, and elevated parathyroid hormone, leading to a higher risk of osteoporosis, myelofibrosis, and other bone diseases[3,4]. According to prior research and experience from clinical practice, the pathogenesis and potentially the treatment of renal anemia and abnormal bone metabolism may have many interactions [5]. For example, improving the hematopoietic microenvironment of bone marrow can be achieved by improving bone metabolism. When anemia is corrected, the oxygenation of bone tissues is expected to improve, leading to better bone function.

Hypoxia-inducible factor (HIF) is a heterodimeric transcriptional factor that can induce the production of EPO and oxygen-sensitive genes under the hypoxic environment. HIF-prolyl hydroxylase (HIF-PHD) is an enzyme that regulates the stability of the α subunit of HIF through post-translational HIF hydroxylation in an oxygen-

dependent manner, thereby maintaining the balance between environmental oxygen availability and HIF activities. Recent reports have confirmed the pivotal role of HIF-PHD as a critical gatekeeper overseeing the process of coordinated transcriptional adaptation to hypoxia and oxidative stress; its unique physiological position renders it a suitable therapeutic target for managing renal anemia. Inhibitors of HIF-PHD have been tested and validated as a viable therapeutic option clinically[6-8]. However, the hypoxic regulation of bone metabolism regarding bone maturation and osteoblast differentiation remains poorly understood, although hypoxia is expected to participate in the pathogenesis of both anemia and abnormal bone metabolism. There is still a lack of effective treatment options for the simultaneous occurrence of anemia and abnormal bone metabolism.

Therefore, the present study aimed to clarify the bidirectional relationship between anemia and abnormal bone metabolism, search for evidence that hypoxia can improve bone metabolism, and provide a new research direction for the treatment of complications in patients with CKD.

MATERIALS AND METHODS

CNKI and PubMed searches were performed using the key words "chronic kidney disease," "abnormal bone metabolism," "anemia," "hypoxia," and "HIF" to identify relevant articles published in multiple languages and fields. Reference lists from identified articles were reviewed to extract additional pertinent articles. Then we retrieved the Abstract and Introduction and searched the results from the literature, classified the extracted information, and summarized important information. Finally, we made our own conclusions. We have expanded the scope of literature search to reduce the risk of bias associated with article selection.

RESULTS

After reviewing 59 studies, we found that abnormal bone metabolism and renal bone disease were connected in the hematopoietic microenvironment. Abnormal vitamin D metabolism and hyperparathyroidism can affect bone metabolism, blood cell production, and survival rates through multiple pathways. Anemia will further attenuate the normal bone growth. According to the study of HIF in the treatment of renal anemia, HIF has more physiological potential. The hypoxic environment regulates bone morphogenetic protein, vascular endothelial growth factor, and neuropilin-1, and affects osteoblast/osteoclast maturation and differentiation through bone metabolic changes. Hypoxia preconditioning of mesenchymal stem cells (MSCs) can enhance their paracrine effects and promote fracture healing. Concurrently, hypoxia reduces the inhibitory effect on osteocyte differentiation by inhibiting the expression of fibroblast growth factor 23. Hypoxia potentially improves bone metabolism, but it still carries potential uncertainty, and the optimal concentration and duration of hypoxia remain unclear.

DISCUSSION

Relationship between abnormal bone metabolism and anemia in the pathogenesis of CKD

Effects of impaired vitamin D metabolism: Inorganic phosphorus within the fluid of cortical tubules increases significantly in patients with CKD, and this increase in phosphorus significantly inhibits the synthesis of $1,25(OH)_2D_3$. The injured kidney is unable to synthesize calcitrio[3,4], and even if calcitriol is synthesized, osteoblastic vitamin D receptors (VDRs) cannot bind to it effectively[9-11]. These pathologic changes serve as triggers of abnormal bone metabolism observed in CKD patients. Furthermore, abnormal lipid metabolism associated with decreased vitamin D stores can aggravate CKD-related osteoporosis in patients with specific physical conditions [12]. In addition, the hematopoietic system, especially hematopoietic stem cells (HSCs) in the bone marrow (BM), are vulnerable to the adverse effects of CKD[13-17]. Bony disorders can damage the BM hematopoietic microenvironment. VDR is also expressed by immunocytes, and VDR activation on these cells enhances their anti-

inflammatory effects and also promotes the proliferation of erythrocyte progenitor cells[18,19]. During the course of CKD, the ability of VDRs to be activated is compromised, and their influence on erythrocyte progenitor cells is diminished. Inflammatory cytokines, which are released in higher quantities during CKD, also stimulate the liver to produce hepcidin[20,21], resulting in iron deficiency anemia. Earlier studies have confirmed that vitamin D is effective against abnormal bone metabolism in patients with CKD, and is widely used clinically. Icardi *et al*[22] showed that low hemoglobin (Hb) levels and EPO resistance in patients with CKD were associated with vitamin D deficiency. Along these lines, it is plausible that vitamin D supplementation in patients with CKD can ameliorate erythrocyte damage, increase Hb levels, and reduce EPO resistance, thereby improving symptoms related to anemia (Figure 1).

Anemia and abnormal bone metabolism can be caused by secondary hyperparathyroidism: With the increase of parathyroid hormone (PTH) during CKD, the generation of early erythroid progenitor cells is inhibited. PTH potentially antagonizes EPO production[23], increases the osmotic brittleness of erythrocytes, and impairs their survival[24]. In patients with CKD, elevated PTH causes accelerated bone turnover and is associated with myelofibrosis[25,26], which reduces the production of EPO and aggravates anemia. Moreover, due to the positive correlation between erythroferrone (ERFE) and EPO and lower endogenous EPO production, the inhibition of hepcidin mediated by ERFE is reduced, which also aggravates anemia[27]. Cinacalcet, a calcimimetic for treating secondary hyperparathyroidism (SHPT), has been shown to attenuate the inhibitory effects on erythrocytes posed by PTH[6,28,29], reduce the amount of EPO required for correcting anemia in patients with CKD[30], and improve bone integrity in such patients[31]. Cinacalcet can simultaneously optimize their BM hematopoietic microenvironment[32]. After parathyroidectomy (PTX), the required EPO dose in patients with CKD-related anemia significantly declines[33]. Together, these findings suggest that surgical or medical treatments directed toward SHPT and associated abnormal bone metabolism can potentially improve symptoms related to anemia (Figure 1).

Abnormal bone metabolism can be exacerbated by anemia: Due to the complications of abnormal calcium and phosphorus metabolism, patients with CKD frequently have osteodystrophy. Anemia will further attenuate the normal bone growth and affect the formation of bone marrow as well as the generation of hematopoietic stem cells. This constitutes a vicious circle.

Effects of hypoxia on anemia and abnormal bone metabolism in patients with CKD

Patients with CKD invariably suffer from a status of low tissue oxygen tension. Hypoxia is a common precipitator of abnormal bone metabolism and anemia. Because HIF-PHD inhibitors (HIF-PHI) have been used to treat renal anemia and abnormal bone metabolism interacts with anemia, it is possible that HIF-PHIs exert similar therapeutic efficacy against bone disease in patients with CKD. In the following sections, we will provide several unifying theories to support this therapeutic plausibility.

Hypoxic environment and anemia: Hypoxia may occur during episodes of microcirculatory insufficiency and hypoperfusion involving different tissues, including the kidney[34,35]. Studies have shown that the pathogenesis of CKD might include the loss of coherence within the microvascular network, resulting in an aberrantly heterogeneous pattern of focal microvascular rarefaction; this abnormality could diminish local blood flow velocity, relax vessel tone, and impair the oxygen uptake of tissues. From this perspective, tissue hypoxia is not uncommon during CKD[36,37]. Furthermore, chronic hypoxia by itself constitutes a vicious cycle, in which inflammatory cells are recruited and aggregate locally, promoting tissue fibrosis and further aggravating tissue hypoxia and organ damages[38,39]. On the other hand, anemia in patients with CKD is associated with destruction of the BM hematopoietic microenvironment. BM is widely considered to be a relatively hypoxic tissue[13], due to the finding that the low oxygen environment can optimize HSC activity[40,41] and improve anemia. The discovery of this hematopoiesis machinery facilitates the subsequent development of HIF-PHIs as a new treatment strategy for renal anemia. Under hypoxic conditions, the mechanisms by which treatment of renal anemia is accomplished predominantly involve the manipulation of HIF-α and PHD. HIF-2 regulates the expression of divalent metal transporter 1 (DMT1) and duodenal cytochrome b (Dcytb), thereby inhibiting the production of hepcidin in the liver. Dcytb has been shown to reduce dietary Fe^{3+} to Fe^{2+}, which is transported by DMT1 later to small intestinal epithelial

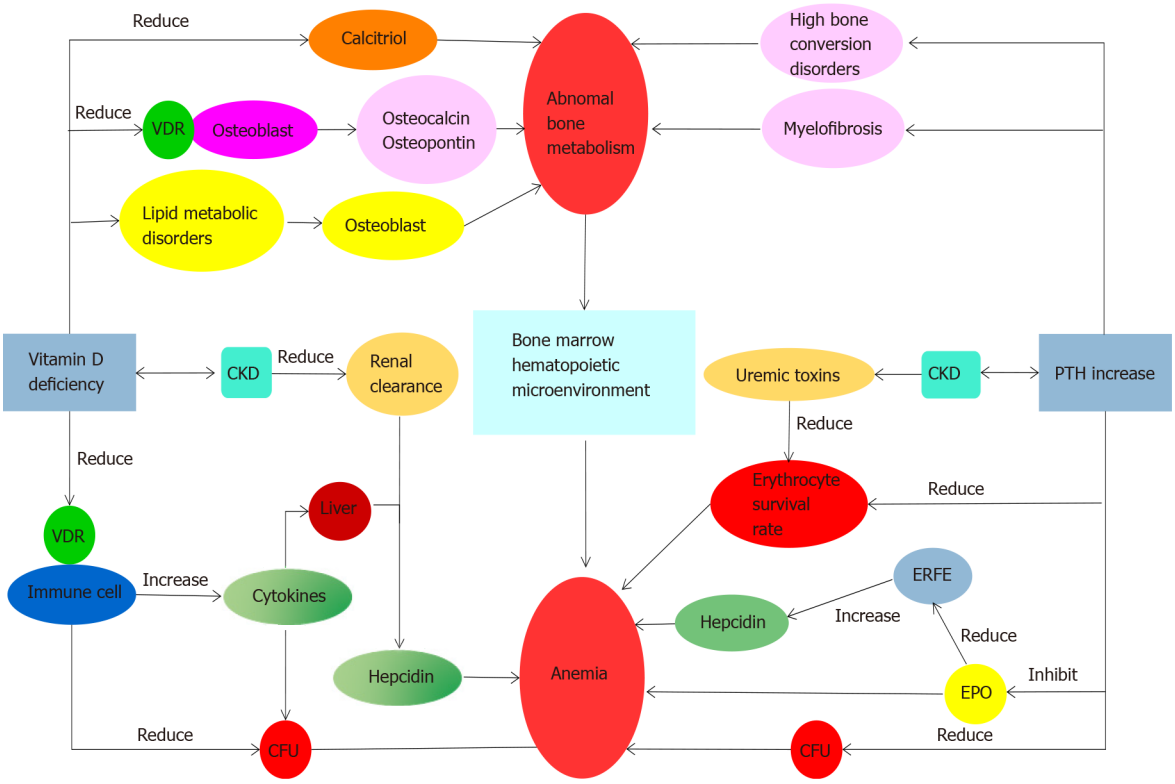

Figure 1 The pathogenetic relationship between anemia and abnormal bone metabolism in patients with chronic kidney disease. CFU: Colony-forming unit; VDR: Vitamin D receptor; PTH: Parathyroid hormone; EPO: Erythropoietin; ERFE: Erythroferrone.

cells for storage in the liver, small intestine, and macrophages. In addition, HIF-1 induces the expression of transferrin (Tf), transferrin receptor 1, and ferroportin (FPN), facilitating the transportation of iron stores to BM. HIFs also bind to the hypoxia responsive element within the promoter area of the EPO gene, and directly stimulate endogenous EPO production. Through the decrease of hepcidin, HIFs improve iron transportation[42] and increase BM iron stores, resulting in anemia improvement. In the backdrop of this complicated scene, PHD is key to the regulation of the HIF pathway. During hypoxia, PHD2 is inactivated and HIF degradation is inhibited. In line with these findings, HIF-PHI has been shown to stabilize HIF-α and increase the expression of downstream targets[43]. The therapeutic advantage of HIF-PHI over conventional EPO for renal anemia lies in the fact that HIF-PHI is more physiologically directed relative to EPO[44].

Hypoxic environment and bone development: Hypoxia exhibits complex effects on bone metabolism. Heterotopic ossification (HO) refers to the formation of bone-like tissues outside the skeletal system, and the process of adaptation to a hypoxic microenvironment is a powerful driver for the development of HO. The hypoxic microenvironment increases the stability of HIF-1α, which regulates a coordinated network consisting of bone morphogenetic proteins, vascular endothelial growth factor, and neuropilin-1, all of which are implicated in the formation of ectopic bone-like tissues[45]. Existing studies have found that the severity and duration of hypoxia to which tissues are exposed and the stage of osteoblast differentiation during which hypoxia occurs may influence bone growth and reconstruction.

In an environment of low oxygen level, pathways involved in bone metabolism are altered, which affect the maturation and differentiation of osteoblasts/osteoclasts. For osteoblasts, hypoxia predominantly occurs during their early stage of differentiation, and hypoxia facilitates premature osteoblast differentiation with incorrect signals produced for stimulating matrix maturation and mineralization[46,47]. Through up-regulating HIF-1α, short-term hypoxia enhances matrix mineralization, promotes osteoblast differentiation and maturation, and accelerates osteogenesis[48-51]. For osteoclasts, hypoxia increases osteoclast production irrespective of the differentiation stage during which hypoxia occurs, but the duration and severity of hypoxia may influence osteoclast differentiation. During hypoxia, anaerobic metabolism becomes predominant with acidic metabolites accumulation, causing mild acidosis of the local

microenvironment and driving the activation of osteoclasts[52]. The regulatory relationship between HIF and adenosine A2B receptors in the hypoxic microenvironment can also enhance glycolysis and alter mitochondrial metabolism within osteoclasts, increasing the likelihood of bone absorption[53].

CKD patients with abnormal bone metabolism, especially those who are older, are at a higher risk of developing pathological fractures due to aberrant bone metabolism and the co-existing osteoporosis. Prior studies have demonstrated that hypoxic preconditioning of MSCs can enhance their paracrine effects by increasing the production of exosomal miR-126 through activating HIF-1α; hypoxia-treated exosomes promote bone fracture healing through exosomal miR-126[54].

FGF23 is mainly secreted by osteocytes. The bone-derived FGF23 acts in concert with PTH and active vitamin D calcitriol to regulate calcium and phosphate homeostasis. Overexpression of FGF23 inhibits osteoblast differentiation and bone matrix mineralization[55]. Experimental studies have shown that in rat preosteoblasts, $1,25(OH)_2$-D-induced FGF23 expression is completely repressed under hypoxic conditions (0.2% O_2) for 24 or 48 h, while hypoxia alone fails to trigger FGF23 expression [56]. Therefore, hypoxia can reduce the inhibitory effect on osteocyte differentiation by inhibiting FGF23 expression. α-Klotho is also an important factor affecting bone metabolism. However, whether hypoxia affects bone metabolism by manipulating α-Klotho expression remains unclear.

Current guidelines for treating bone diseases fail to consider the control of hypoxia as a therapeutic option. Sustained and intermittent hypoxia may inhibit osteogenic differentiation and promote osteoclast function, and cyclic hypoxia has been proposed as a promising strategy for favorably affecting bone metabolism. Exposure to moderate oxygen concentration (> 2% *in vitro* and 9%–16% *in vivo*) persistently over days to weeks may increase bone mineralization potential, inhibit osteoclastic activity, and/or stimulate osteoblastic action[57]. In fact, hypoxia may potentially improve bone metabolism, but the underlying side effects should not be neglected, including the induction of senescence involving bone marrow mesenchymal stem cells and the risk of bone metastases in patients with cancer. Additional research is necessary to discover and test the optimal regimen of cyclically exposing tissues to certain oxygen concentration and the time required for exposure (*e.g.*, the duration, length, and frequency of exposures per day).

Delaying CKD progression reduces complications: Li *et al*[58] studied the stress response of renal tubules to hypoxia and found that during the transition from acute kidney injury to CKD, the absence of forkhead box O3 in renal tubules led to the deterioration of tubular structure and function, manifesting as a more severe CKD phenotype. In hypoxic kidneys, transcription factors associated with stress responses can be activated to ameliorate hypoxic injury and reduce the risk of progression to CKD.

Previous studies have shown that HIF-1 restricts the anabolic actions of PTH[59]. In the bidirectional relationship between anemia and abnormal bone metabolism (Figure 1), lowering PTH can improve anemia and abnormal bone metabolism through multiple pathways. Although there is no clear evidence that HIF enhances vitamin D metabolism, HIF can act separately on several downstream pathways including calcitriol transformation, osteoblasts and osteoclasts growth and development, EPO production, and iron transport. Unfortunately, due to the limited evidence available, currently there is no therapeutic approach related to hypoxia for promoting bone metabolism. It is expected that potential HIF subtypes and pathways involved in the hematopoietic system and bone metabolisms will be discovered in the future.

CONCLUSION

This review summarizes findings from recent studies on renal anemia and abnormal bone metabolism in patients with CKD. Mounting evidence supports the notion that there is a connection between both CKD complications, ranging from their pathogenesis to viable therapeutic strategies. Several reports have shown that hypoxia can improve anemia and delay the progression of CKD, and hypoxia-targeted treatments such as HIF-PHIs are starting to be used clinically for anemia. Moreover, there is also evidence that hypoxia potentially improves bone metabolism, although the exact degree of low oxygen concentration and the duration required for obtaining results remain uncertain, necessitating further studies. Anemia and abnormal bone metabolism adversely influence patient prognosis. To improve the quality of life of patients with CKD, future studies should address the effect of HIF on bone metabolism while

treating anemia, and HIF may be a useful treatment for improving the prognosis of patients with CKD.

ARTICLE HIGHLIGHTS

Research background

Abnormal bone metabolism and renal anemia seriously affect the prognosis of patients with chronic kidney disease (CKD). Currently, there are few studies on the evaluation of their mutual connection. With the availability of hypoxia-inducible factor (HIF) stabilizers, more therapeutic choices for renal anemia are expected in the future. However, the effects posed by the hypoxic environment on abnormal bone metabolism remain incompletely understood. If we can find evidence that HIF could improve both complications, it will be a great advantage to improve the prognosis of patients with CKD.

Research motivation

The purpose of this article is to summarize the relationship between renal anemia and abnormal bone metabolism, and to discuss the influence of hypoxia on bone metabolism, in order to provide a new way of thinking for the future studies on the treatment of CKD complications.

Research objectives

To clarify the bidirectional relationship between anemia and abnormal bone metabolism, to find evidence that hypoxia can improve bone metabolism, and to provide a new research direction for the treatment of complications in patients with CKD.

Research methods

We searched relevant articles published in multiple languages and fields, summarized important information, and drew our conclusions.

Research results

Anemia and bone metabolism interact. The hypoxic environment could affect osteoblast/osteoclast maturation and differentiation, enhance the paracrine effect of mesenchymal stem cells, and reduce the inhibitory effect of fibroblast growth factor 23 on osteocyte differentiation. Hypoxia potentially improves bone metabolism, but the optimal concentration and duration of hypoxia remain unclear and need further study.

Research conclusions

There is a bidirectional relationship between renal anemia and abnormal bone metabolism. The relationship has rarely been studied. Hypoxia may improve bone metabolism, but the concentration and duration of hypoxia remain unclear and need further study. To improve the quality of life of patients with CKD, future studies should address the effect of HIF on bone metabolism while treating anemia, and HIF may be a useful treatment for improving the prognosis of patients with CKD.

Research perspectives

In future studies, we can focus more on the exact degree of hypoxia concentration and duration required for improving bone metabolism.

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