

Does Physical Exercise Ameliorate Chronic Kidney Disease-Related Complications? The Case of Anaemia and Chronic Kidney Disease-Mineral Bone Disorder

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Keywords

Physical exercise · Chronic kidney disease · Dialysis ·
Chronic kidney disease-mineral bone disorder · Anaemia

Abstract

Background: Physical exercise (PE) can regulate inflammation, cardiovascular health, sarcopenia, anaemia, and bone health in the chronic kidney disease (CKD) population. Experimental and clinical studies both help us better understand the mechanisms that underlie the beneficial effects of the exercise, especially in renal anaemia and CKD-mineral bone disorders (CKD-MBDs). Here, we summarize this evidence, exploring the biological pathways involved, locally released substances, and crosstalk between tissues, but also the shortcomings of current knowledge. **Summary:** Anaemia: Both in healthy and CKD subjects, PE may mimic hypoxia, inhibiting PHDs; so hydroxylate HIF- α subunits may be translocated into the nucleus, resulting in dimerization of HIF-1 α and HIF-1 β , recruitment of p300 and CBP, and ultimately, binding to HREs at target genes to cause

activation. However, in CKD subjects acute PE causes higher levels of lactate, leading to iron restriction by upregulating hepatic hepcidin expression, while chronic PE allows an increased lactate clearance and HIF- α and VEGFa levels, stimulating both erythropoiesis and angiogenesis. CKD-MBD: PE may improve bone health decreasing bone resorption and increasing bone formation throughout at least three main pathways: (a) increasing osteoprotegerin and decreasing RANKL system; (b) decreasing cytokine levels; and (c) stimulating production of myokines and adipokines. **Key Messages:** Future research needs to be defined to develop evidence-based exercise guidance to provide optimal benefit for CKD using exercise interventions as adjuvant therapy for CKD-related complications such as anaemia and CKD-MBD.

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Published by S. Karger AG, Basel

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Introduction

Sedentary behaviour is nowadays the fourth leading risk factor for global mortality because it is involved in developing cardiovascular disease, type 2 diabetes, arterial hypertension, obesity, and premature death [1]. Also, in the chronic kidney disease (CKD) population, physical activity (PA) and physical exercise (PE) are related to clinical outcomes [2] and are now suggested by consensus papers [3, 4] and by recent clinical practice guidelines for exercise and lifestyle in CKD [5] that summarizes the evidence for the benefits of regular exercise participation for people with all stages of kidney disease. Regular exercise promotes a shift towards a less inflammatory immune cell phenotype. It reduces chronic systemic inflammation, likely contributing to improved left ventricular hypertrophy, insulin sensitivity, skeletal muscle mass, and bone mineral density (BMD). Many experimental and clinical studies have shown that PE can regulate inflammation, cardiovascular health, lipid metabolism and insulin resistance, sarcopenia, and bone health in CKD [6]. In fact, even in the CKD population, PE offers protective benefits for the maintenance of health and function with age [7]. Intervening through the means of PA and/or PE in this population may provide an opportunity for the alleviation of symptoms in the short term, improving quality of life, but also benefitting patient outcomes by counteracting the main CKD-related complications such as anaemia [8] and CKD-mineral bone disorder (CKD-MBD) [6]. The present paper aimed to describe the responses and adaptations to exercise in relevant biological systems such as bone metabolism and erythropoiesis.

Blood, Oxygen, and PE

Physical work capacity, maximum oxygen consumption, and endurance performance capacity in humans greatly depend on the efficient transport of oxygen to working tissues. The capillary-to-myofiber interface guarantees the delivery of oxygen and nutrients, which are crucial for muscle function. It describes the strong correlation between skeletal muscle capillary density and muscle oxygen conductance in rats selectively bred for running endurance [9]. A greater erythropoietin (EPO) response is seen in several athletes undergoing intense resistance exercise and long and powerful aerobic exercise. This EPO increase appears to be transient [10]. Together with high hypoxia-inducible factor (HIF)-1 α , protein levels increased immediately after exercise-induced hypoxia, and mRNA levels for HIF-1 target genes EPO and vascular endothelial growth factor A

(VEGF-A) were also higher post-exercise [11]. Therefore, in addition to increased erythropoiesis, VEGF-A promotes angiogenesis, a well-described tissue adaptation of the skeletal muscle tissue to endurance training. Interestingly, in trained muscles, HIF-1 α and VEGF-A are low, probably related to reduced exercise-induced hypoxic stress and enhanced muscle blood flow [12].

Anaemia as a Disease or Sign?

According to the World Health Organization (WHO), anaemia is a haemoglobin concentration lower than 13 g/dL in men and lower than 12 g/dL in women [13]. It is better defined as a low blood haemoglobin concentration, irrespective of the underlying cause, red blood cell morphology, or function, based on age, sex, and physiological status [14]. Anaemia results in symptoms such as fatigue, weakness, dizziness, and shortness of breath. Fatigue is a commonly reported and debilitating symptom among patients with CKD and may begin affecting quality of life as early as CKD stage 2. Even if the pathophysiology of fatigue in CKD is multifactorial, anaemia could play a crucial role [15]. Renal anaemia is typically normocytic, normochromic, and hyperproliferative due to relative EPO deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis.

Functional iron deficiency is characterized by an “inflammatory block” with TSAT $\leq$ 20% and elevated ferritin levels. Hepcidin, a protein produced by hepatocytes and, in a small quantity, by macrophages and adipocytes, is responsible for iron enteric absorption and iron transportation by stimulating ferroportin expression. While hepcidin levels decrease in hypoxia in physiological conditions, their synthesis increases during periods of infection or inflammation [16].

Hepcidin excess may account for the impaired dietary iron absorption and reticuloendothelial cell iron blockade present in many CKD patients. It binds and induces degradation of the iron exporter, ferroportin, on duodenal enterocytes, reticuloendothelial macrophages, and hepatocytes to inhibit iron entry into the plasma. Inflammatory cytokines directly induce hepcidin transcription, presumably as a mechanism to sequester iron from invading pathogens, leading to the iron sequestration, hypoferremia, and anaemia that are hallmarks of many chronic diseases including CKD [16].

Advanced CKD is characterized by persistent low inflammation and endothelial dysfunction due to high serum levels of uremic toxins, such as indoxyl sulphate and p-cresol, contributing to renal anaemia [17, 18]. This

condition is also responsible for 5–10% of patients with end-stage renal disease exhibiting hyporesponsiveness to EPO-stimulating agents (ESAs) [19].

How PE May Affect Renal Anaemia

Intensive PE increases blood lactate concentration, which represents an expression of the metabolic cellular stress, namely, a transient shift from an aerobic to anaerobic glycolysis to produce cellular energy in a hypoxic background. In a normal condition, lactate clearance is promoted during the active or passive recovery [20]. CKD patients present very little tolerance to exercise due, among other reasons, to the accumulation of the body's waste products, anaemia, and muscle mass loss. This condition leads to lower PA levels than the general population [21]. Besides, they have more difficulty washing out blood lactate after PE than healthy subjects [22]. Nevertheless, Meierhenrich et al. [23] showed a decrease in lactate and excess lactate associated with the rise of haemoglobin immediately after PE in a group of dialysis patients. The correction of renal anaemia with ESA improves but does not normalize maximal PE capacity because of an abnormal energy metabolism already seen in the pre-dialysis stages, explained by the presence of progressive and degenerative low inflammation [24].

PE could be a valid strategy to prevent and improve renal anaemia in this setting. According to several studies, aerobic and resistance exercise are valid alternatives to improve functional capacity and quality of life in CKD patients (fatigue, above all) [25]. Aerobic and resistance exercise can also stimulate HIF α , increasing the possibility of exercise training becoming a relevant treatment for anaemia in older people with end-stage renal disease [26]. The proposed mechanisms are detailed in Figure 1.

Exercise and Renal Anaemia, Future Perspectives

The introduction of HIF-PH inhibitors also defined as HIF1 α stabilizers represents this century's milestone for anaemia treatment in CKD patients [27]. There is evidence that HIF stabilization may downregulate the production of hepcidin. Nowadays, we know that endogenous EPO is more effective than ESA in stimulating erythropoiesis and pleiotropic effects in other tissues. PE in a short period ameliorates EPO production and promotes muscle synthesis and angiogenesis closely correlated with the enhancement of haemoglobin levels. Further research on long periods of observation could evaluate the synergy between novel anaemia treatments and regular PE.

The Bone Is an Endocrine Organ

Today, advanced research methods provide new understandings of the bone as a crucial endocrine organ, its role being much more than mechanical coupling. Bone and extraosseous organs, including heart and brain, have complex and precise communication mechanisms. For example, fibroblast growth factor (FGF) 23, lipocalin-2 (LCN2), and osteocalcin (OCN) are three representative bone-derived cytokines involved in energy metabolism, endocrine homeostasis, and systemic chronic inflammation levels [28, 29]. Bone is now recognized as a secretory organ, and regulation of bone metabolism occurs through osteokines and bone-derived factors via autocrine, paracrine, and endocrine systems [30]. On the one hand, the inflammatory cytokine interleukin-6 activates the secretion of osteoblast and osteocyte-induced receptor activator of nuclear factor- κ B (RANK), which drives osteoclastogenesis. RANKL then binds to its receptor, inducing osteoclast differentiation.

On the other hand, osteoprotegerin (OPG) inhibits the RANK-RANKL interaction and prevents osteoclastogenesis, restraining bone loss [31]. The dysregulation of the RANK-RANKL-OPG axis can lead to osteoporosis. In the CKD setting, OPG concentrations have consistently been reported to be higher, probably due to a compensatory protective mechanism to moderate bone remodelling, while RANKL levels have shown conflicting findings. In conjunction with a systemic anti-inflammatory effect, several osteokines are released in response to exercise training, exerting favourable physiological and metabolic effects in skeletal muscle and bone. Osteocalcin, OPG, and IGF-1 are upregulated by exercise, while no apparent effects are reported for FGF-23, sclerostin, and RANK-RANKL.

PE and Bone Health

Regular PA has a crucial role in bone strengthening in the general population. PA affects bone metabolism, resulting in an adaptation of bones in terms of shape, mass, and strength to mechanical loading [31]. Higher levels of PA are widely accepted to promote bone health across the lifespan by improving bone mass in growing children and decreasing bone loss in older adults. PA, therefore, reduces the risk of osteoporosis and bone fractures. It has been accepted that mechanical forces help promote bone mass and strength. The so-called *Mechanostat Theory* expresses that bones have their innate biological system to induce bone formation in response to mechanical forces [32]. The mechanical strain acts on osteoclasts and osteoblasts, regulating the skeleton homeostasis [33].

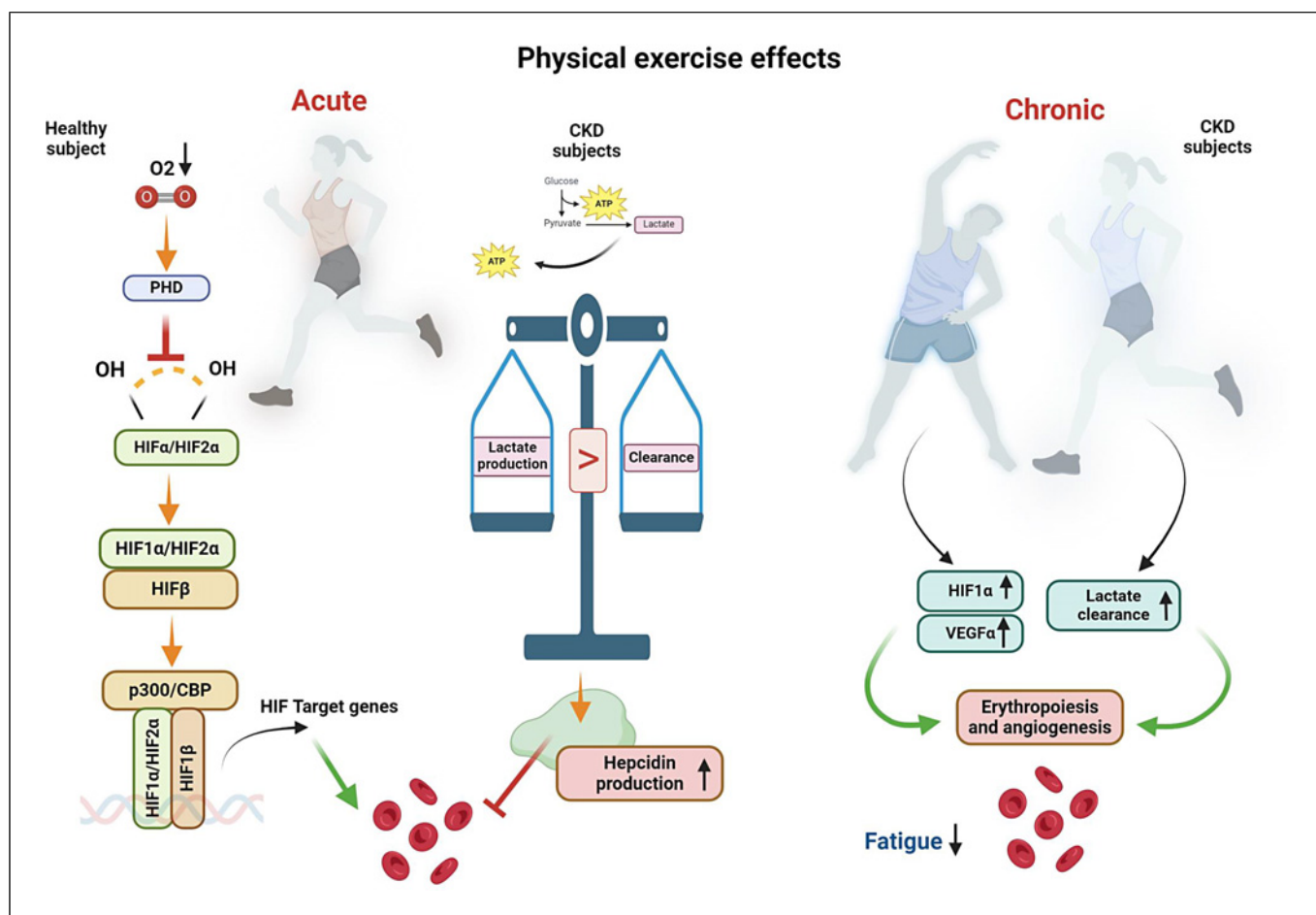


Fig. 1. Possible effects of PE on renal anaemia. In normal conditions, HIF1/2 are hydroxylated by prolyl hydroxylase domain (PHD)-containing enzymes and then degraded in the proteasomes via polyubiquitination. PE in acute conditions may mimic hypoxia, inhibiting PHDs; so hydroxylate HIF- α subunits may be translocated into the nucleus, resulting in dimerization of HIF-1 α and

HIF-1 β , recruitment of p300 and CBP, and ultimately, binding to HREs at target genes to cause activation. In CKD subjects, acute PE causes higher levels of lactate, leading to iron restriction by up-regulating hepatic hepcidin expression. The chronic effects of PE in CKD subjects are increased lactate clearance and HIF- α and VEGF α levels, stimulating both erythropoiesis and angiogenesis.

Moreover, mechanical load as an exercise regulates collagen synthesis during bone formation. Muscle tension is transferred to the bones and leads to provoking osteoblast proliferation. On the contrary, sedentary behaviour would reduce osteoblast activity and increase osteoclast function. PA/PE positively affects bone metabolism via different mechanisms [34].

1. *Activation of an inflammatory cascade* involving cells of the innate and adaptive immunity and mediators of inflammation; PA activates an inflammatory cascade involving cells of the innate and adaptive immunity, as cytokines and mediators of inflammation, as myokines and adipokines, which create an environment adapt for recovery, regeneration, and adaptation of the

bone. In particular, irisin, a myokine involved in glucose and bone homeostasis, is increased after PE and may have a protective role because it correlates with BMD and bone strength.

2. *Triggering an immunological response* due to the increase of interleukin-6 by skeletal muscle; PE activates the inflammasome complexes, triggering the release of IL-10, a potent anti-inflammatory molecule. Acute PE increases pro-inflammatory cytokines, whereas regular exercise results in an enhancement of anti-inflammatory molecules.
3. *In stimulation of the Wnt signalling pathway*; osteocytes can respond to physical stimulation directly by using various mechanosensors, such as Wnt signalling

components. The function of osteocytes in response to mechanical stimulation from exercise is also regulated indirectly by extracellular cytokines ranging from RANKL/OPG to sclerostin. Bone cell mechanotransduction is a complex process that involves several pathways leading to bone formation, of which the Wnt- β -catenin cascade is one of the most prominent; this pathway is negatively regulated by endogenous secreted inhibitors such as sclerostin, downregulated by mechanical loading, and upregulated by mechanical disuse.

PE suppresses osteoclastogenesis and bone remodeling, mediated through the OPG/RANKL pathway released by osteoblasts and osteocytes. In most studies reviewed by Tobeiha et al. [33], PA/PE promote bone health by increasing OPG and decreasing RANKL levels.

Thus, there are direct and indirect regulation mechanisms of PA on bone health: the former are mediated by cell surface receptors, the starting point for understanding the regulatory effects of mechanical loading, which include integrins, connexin, polycystins, Wnt signalling, and sclerostin. The latter includes exercise-induced regulation of bone environment through cytokines, including inflammatory factors and myokines, such as irisin. These factors affect bone remodelling, promoting bone mass and sustaining healthy bone. PE, through its direct or indirect effects, can change biochemical markers of bone turnover and, consequently, bone mass; that is the reason why it is suggested in the different forms of osteoporosis [35].

How CKD-MBD Affects Bone Health

Bone is now recognized as an endocrine organ at the heart of CKD-MBD, a systemic mineral and bone metabolism disorder manifested by various laboratory, bone, and vascular abnormalities [36]. It is a potent risk factor for cardiovascular morbidity and mortality throughout left ventricular hypertrophy, arrhythmia, and cardiovascular calcification.

Changes in bone tissue occur from early CKD stages, mainly related to increased sclerostin and FGF23 levels, two molecules secreted by osteocytes, and the consequent repression of the Wnt- β catenin signalling pathway. Increasing PTH, to a certain extent, may thus appear as an adaptive mechanism to maintain normal serum calcium, phosphate, and/or calcitriol levels and a routine bone remodelling. In fact, during CKD, secondary hyperparathyroidism is quite common. Although intermittent high levels of PTH can exert an anabolic effect on bone, its

constant elevation increases bone remodelling, exerting a catabolic effect on cortical and trabecular bone [36].

The two most common histologic patterns derived from altered PTH levels are osteitis fibrosa, high PTH, and adynamic bone disease (ABD), low levels. The persistent and constant elevated PTH increases the bone resorption units, leading to negative bone balance; the increased osteoblastic activity does not have an orderly and laminar disposition, as in normal bone, and is defined as woven bone. The overall result is a loss of cortical bone secondary to the accelerated resorption, which far exceeds bone formation, and in the place of laminar osteoid, fibrous tissue even containing cysts is present [37]. On the other hand, ABD is characterized by suppressed bone formation, low cellularity, and thin osteoid seams. The last one mentioned is the most crucial difference with osteomalacia (comprehensive osteoid volume) since mineralization is normal in ABD. The prevalence of ABD has increased significantly in the last years, and in most recent studies, it is described as the most prevalent histologic pattern, probably due to the patient's increasing age and a higher prevalence of diabetes mellitus-related hypoparathyroidism. This condition has also been associated with higher mortality, occasionally attributed to an increased number of fractures and accelerated vascular calcification [38]. In summary, CKD-MBD has a relevant impact on bone health, which is no longer just represented by bone remodelling disorders. It is associated with a higher risk of falls and fractures and higher mortality rates when a fracture occurs.

How PE May Affect CKD-MBD

Recent experimental [39] and clinical [40] evidence indicates that PA/PE may influence CKD-MBD throughout at least three main biological pathways. During the course of CKD, levels of sclerostin are inversely related to the declining GFR, and the Wnt- β -catenin pathway is downregulated [39]. One study in haemodialysis patients showed a reduced sclerostin level and increased BMD after dynamic resistance training performed before each dialysis session for 6 months [40]. Exercise-related improvements in BMD and reduced bone loss may be mediated via decreased sclerostin release from bone either directly and/or via reduced skeletal muscle myostatin mRNA expression. Exercise-mediated decreases in the release of FGF23 and increases in klotho release in bone might also contribute to improved BMD and reduced bone loss. These potential mechanisms are based on the available data from studies of the effects of short-term exercise intervention

in patients with CKD, kidney failure on dialysis, and kidney transplant recipients.

It is well known that CKD is characterized by an increased osteocyte production of secreted factors, including the anti-anabolic protein sclerostin. Elevated sclerostin is associated with reduced Wnt/ β -catenin signalling in bone and decreased osteoblast differentiation/activity [41]. Wnt signalling cascade is a cell biological pathway involved in bone cell mechanotransduction, PA exerting a mechanical stimulation that may improve skeletal integrity and reduce fracture risk [39]. This suggests that modulation of the Wnt signalling pathway holds great promise in altering bone mass and mimicking some of the positive effects of mechanical strain on bone throughout the downregulation of sclerostin, also becoming a target for pharmacological intervention.

On the other hand, dynamic resistance exercise training in haemodialysis patients was shown to reduce sclerostin levels [39]. Unfortunately, the other two studies did not confirm these results [42, 43], although the first reported an increase in bone alkaline phosphate, which is suggestive of increased osteoblast activity [42].

Another biological pathway involved in osteoclast differentiation and bone resorption is the RANKL-RANK-OPG system. In CKD, the RANKL-RANK-OPG system favours bone resorption as PTH upregulates RANKL and downregulates OPG [44]. By contrast, exercise might inhibit bone loss by reducing RANKL and/or increasing OPG [45]. Intradialytic resistance exercise may increase plasma OPG levels and improve BMD, suggesting that the increase in OPG levels might contribute to the prevention of bone loss in CKD patients [42, 46].

The third pathway involves FGF, FGF receptors, and the co-receptor klotho, an essential component of endocrine FGF receptor complexes that governs multiple metabolic processes in mammals, known to be involved in premature ageing as an ageing suppressor; the course of CKD is characterized by reduced levels of klotho and increased levels of FGF23 and PTH. PE may increase klotho levels and reduce levels of FGF23 and PTH in both CKD [47] and haemodialysis patients [40]. The proposed mechanisms are detailed in Figure 2.

Experimental and Clinical Evidence

In rats with mild CKD induced by partial nephrectomy, exercise and 8 weeks of treadmill running have been shown to improve BMD and bone microstructure in mild CKD by inhibiting sclerostin production [48]. Micro-CT scanning demonstrated that the CKD exercise-group rats had a higher BMD of the spine and femoral

metaphysis and higher femoral trabecular bone volume than the CKD-group rats. Moreover, serum concentrations of the bone resorption marker CTX-1 were higher in rats from the CKD group and showed an improvement in rats from the CKD exercise group, indicating that exercise alleviated bone resorption in the rats with mild CKD [48].

Another study in a CKD rat model tested the hypothesis that voluntary wheel running would improve musculoskeletal health [49]. The CKD rats with voluntary wheel access showed reduced cortical porosity and improved bone microarchitecture detected by micro-CT scanning, improved muscle strength, increased time-to-fatigue (for VO_2 max), bone mechanics, and with a trend towards reduced vascular calcification and decreased PTH levels.

The effect of exercise on the bone of dialysis patients was investigated in a clinical trial designed to investigate the effect of 12 weeks of progressive resistance training versus 12 weeks of sham-exercise attention control [50]. This kind of intradialytic exercise was associated with improvement in muscle mass, strength, and bone mineral content; these findings were corroborated by another recent trial that demonstrated gains in bone alkaline phosphatase (ALP) over 24 weeks of resistance exercise [51]. The other side of the coin may be seen evaluating the same population's muscle mass and strength on BMD and osteoporosis. Not surprisingly, shorter calf circumference or weaker grip strength was associated with osteoporosis risk and lower BMD among haemodialysis patients, independently of the conventional therapies [52].

Finally, the impact of PA and exercise on bone health in patients with CKD was recently revised by Cardoso et al. [53]. They reviewed six observational (4 cross-sectional, two longitudinal) and seven experimental (2 aerobic, five resistance exercise trials) studies, with an overall sample size of 367 and 215 patients, respectively. The main results were that there is partial evidence supporting (a) a positive relation between PA and bone outcomes and (b) the positive effect of resistance exercise on bone health in CKD. Overall, experimental studies suggest that resistance exercise interventions may improve bone health in CKD stages 3–4, dialysis, and kidney transplant patients; evidence for aerobic exercise is less clear. Moreover, resistance exercise may elicit positive changes in CKD patients' bone metabolism, increasing OPG levels, which may indicate better bone mass and strength. OPG protects bone from excessive resorption and was recently associated with bone fractures in CKD patients [54]. The same is also true for ALP and bone ALP levels [53]. Finally, Yoshioka et al. [55] found that replacing sedentary time with moderate-to-vigorous PA, but not light-intensity PA, improved ultrasound-based

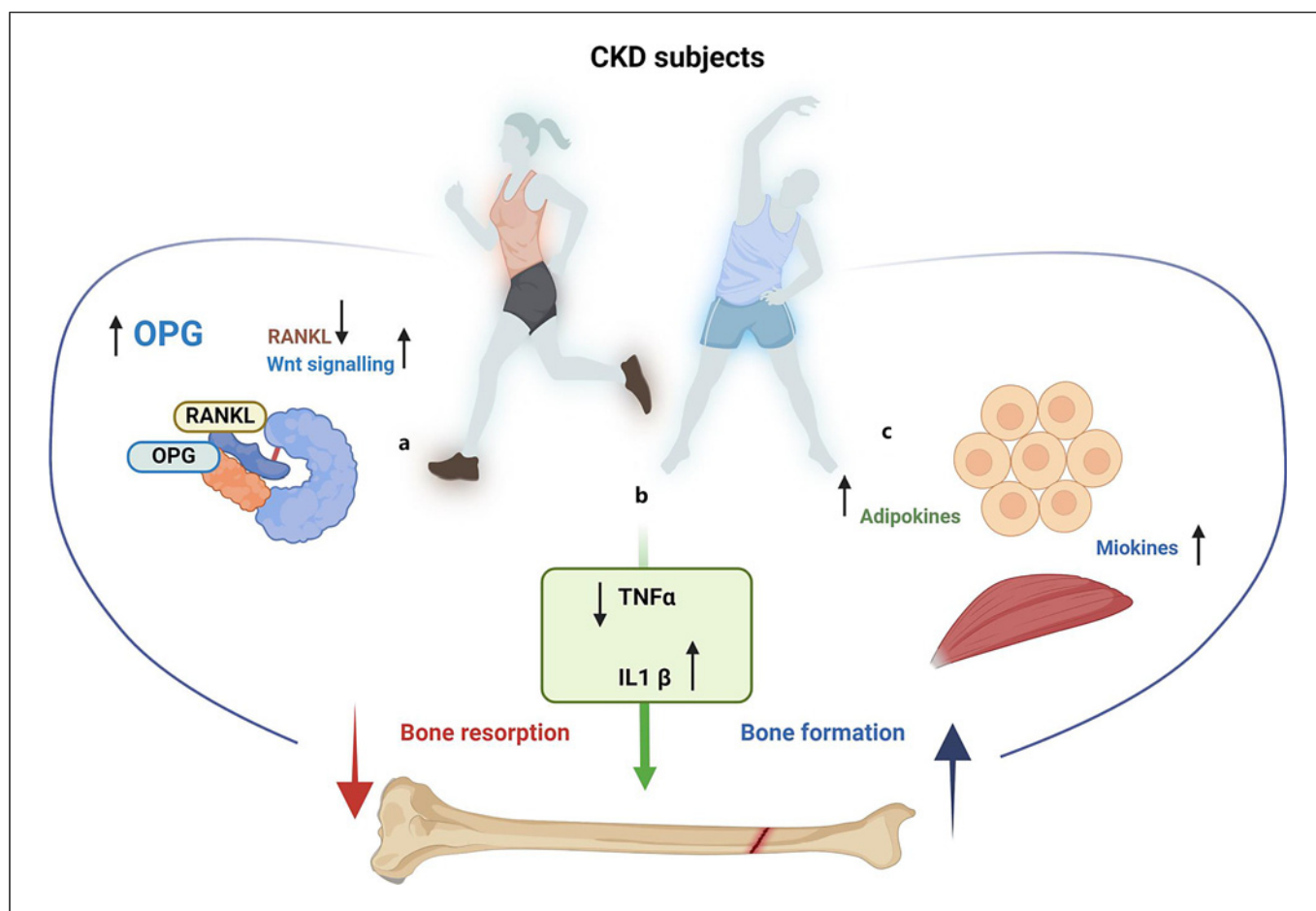


Fig. 2. Possible effects of PE on bone health. PE may improve bone health decreasing bone resorption and increasing bone formation throughout at least three main pathways. **a** Increasing OPG and decreasing RANKL system. **b** Decreasing cytokine levels. **c** Stimulating production of myokines and adipokines.

measures of bone density. Thus, we may suggest resistance exercise in CKD patients to improve BMD at the femoral neck and proximal femur, which may prevent and/or decrease the risk of hip fractures.

Exercise and CKD-MBD, Future Perspective

The current management of CKD-MBD and related fracture risk is based on traditional and novel approaches [56]. Among the latter, it is now recognized that lifestyle factors may influence fracture risk in osteoporosis, and patients with CKD are not exempt from these risks. In this setting, exercise seems to be able to avoid sarcopenia, prevent loss of muscle mass and function, and maintain bone mass through mechanical loading and related biological pathways. Exercise is a non-pharmacological strategy

widely recognized as a vital mechanical stimulus for developing and maintaining optimal bone strength throughout life. The time has come to encourage exercise, maintain physical function, and reduce the risk of falls, considering that resistance training may be particularly beneficial to skeletal health.

Nowadays, it is pretty clear that exercise has beneficial effects on muscle and bone strength and metabolic markers in adults with CKD; exercise-mediated activation of the canonical Wnt pathway, reduced FGF23, and increased klotho release may lead to bone formation, reduced bone loss, and improved BMD; both reported physical function and low scores on tests such as the 6-min walking test are associated with falls and fractures; last but not least, resistance training may (1) elicit a normal, anabolic muscle response, (2) increase BMD, mainly at the peripheral skeleton, and (3) increase whole-body BMC. Although

more research is needed in this field, clinicians and exercise physiologists should advise CKD patients to increase their PA levels as it may be related to higher BMD, apart from other physiological and psychological benefits that may be derived from increasing PA.

Conclusions

Nowadays, it is well known that PA, physical function, and performance are strongly associated with all-cause mortality [2]. The beneficial effects of PA/PE are increasingly recognized in chronic inflammation, cardio-respiratory function, muscle and bone strength, and metabolic markers [6, 7]. Although more research is needed in this field, there is evidence that PE exerts its relevant beneficial effects on the anabolic response in skeletal muscle, bone formation, and improvements in the levels of the bone-derived hormones klotho and FGF23 and erythropoiesis too. Consequently, improving PA and function needs to be part of the routine patient-centred management of the CKD population.

References

- 1 World Health Organization Global recommendations on physical activity for health. Geneva, Switzerland: World Health Organization; 2010.
- 2 Painter P, Roshanravan B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2013;22(6):615–23. <https://doi.org/10.1097/MNH.0b013e328365b43a>
- 3 Aucella F, Battaglia Y, Bellizzi V, Bolignano D, Capitanini A, Cupisti A. Physical exercise programs in CKD: lights, shades and perspectives [corrected]. *J Nephrol*. 2015;28(2):143–50. <https://doi.org/10.1007/s40620-014-0169-6>
- 4 Aucella F, Gesuete A, Battaglia Y. A “nephrological” approach to physical activity. *Kidney Blood Press Res*. 2014;39(2–3):189–96. <https://doi.org/10.1159/000355796>
- 5 Baker LA, March DS, Wilkinson TJ, Billany RE, Bishop NC, Castle EM, et al. Clinical practice guideline exercise and lifestyle in chronic kidney disease. *BMC Nephrol*. 2022;23(1):75. <https://doi.org/10.1186/s12882-021-02618-1>
- 6 Bishop NC, Burton JO, Graham-Brown MPM, Stensel DJ, Viana JL, Watson EL. Exercise and chronic kidney disease: potential mechanisms underlying the physiological benefits. *Nat Rev Nephrol*. 2023;19(4):244–56. <https://doi.org/10.1038/s41581-022-00675-9>
- 7 Gollie JM, Ryan AS, Sen S, Patel SS, Kokkinos PF, Harris-Love MO, et al. Exercise for pa-

- tients with chronic kidney disease: from cells to systems to function. *Am J Physiol Ren Physiol*. 2024;326(3):F420–37. <https://doi.org/10.1152/ajprenal.00302.2023>
- 8 Torres E, Aragoncillo I, Moreno J, Vega A, Abad S, García-Prieto A, et al. Exercise training during hemodialysis sessions: physical and biochemical benefits. *Ther Apher Dial*. 2020;24(6):648–54. <https://doi.org/10.1111/1744-9987.13469>
- 9 Howlett RA, Gonzalez NC, Wagner HE, Fu Z, Britton SL, Koch LG, et al. Selected contribution: skeletal muscle capillarity and enzyme activity in rats selectively bred for running endurance. *J Appl Physiol*. 2003;94(4):1682–8. <https://doi.org/10.1152/japplphysiol.00556.2002>
- 10 Kraemer RR, Kraemer BR. The effects of peripheral hormone responses to exercise on adult hippocampal neurogenesis. *Front Endocrinol*. 2023;14:1202349. <https://doi.org/10.3389/fendo.2023.1202349>
- 11 Ameln H, Gustafsson T, Sundberg CJ, Okamoto K, Jansson E, Poellinger L, et al. Physiological activation of hypoxia inducible factor-1 in human skeletal muscle. *FASEB J*. 2005;19(8):1009–11. <https://doi.org/10.1096/fj.04-2304fje>
- 12 Lindholm ME, Rundqvist H. Skeletal muscle hypoxia-inducible factor-1 and exercise. *Exp Physiol*. 2016;101(1):28–32. <https://doi.org/10.1113/EP085318>
- 13 WHO Scientific Group. Nutritional anemias. Geneva, Switzerland: World Health Organization; 1968. (Technical Report Series No.

- 405). Available from: https://apps.who.int/iris/bitstream/handle/10665/40707/WHO_TRS_405.pdf (accessed on March 27, 2020).
- 14 Global Health Metrics. Anaemia–level 1 impairment. *Lancet*. 2019;393. Available from: https://www.healthdata.org/results/gbd_summaries/2019/anemia-level-1-impairment (Accessed 31 January 2024).
- 15 Gregg LP, Bossola M, Ostrosky-Frid M, Hedayati SS. Fatigue in CKD: epidemiology, pathophysiology, and treatment. *Clin J Am Soc Nephrol*. 2021;16(9):1445–55. <https://doi.org/10.2215/CJN.19891220>
- 16 Gaftor-Gvili A, Schechter A, Rozen-Zvi B. Iron deficiency anemia in chronic kidney disease. *Acta Haematol*. 2019;142(1):44–50. <https://doi.org/10.1159/000496492>
- 17 Stam F, van Guldener C, Schalkwijk CG, ter Wee PM, Donker AJ, Stehouwer CD. Impaired renal function is associated with markers of endothelial dysfunction and increased inflammatory activity. *Nephrol Dial Transpl*. 2003;18(5):892–8. <https://doi.org/10.1093/ndt/gfg080>
- 18 Dou L, Bertrand E, Cerini C, Faure V, Sampol J, Vanholder R, et al. The uremic solutes p-cresol and indoxyl sulfate inhibit endothelial proliferation and wound repair. *Kidney Int*. 2004;65(2):442–51. <https://doi.org/10.1111/j.1523-1755.2004.00399.x>
- 19 Ogawa T, Nitta K. Erythropoiesis-stimulating agent hyporesponsiveness in end-stage renal disease patients. *Contrib Nephrol*. 2015;185:76–86. <https://doi.org/10.1159/000380972>

Acknowledgment

Authors would like to express their gratitude to Dr. Mariateresa Zicarelli for her support in creating the figures.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

Authors did not receive any funding for the present paper.

Author Contributions

Filippo Aucella, Francesco Aucella, and Maria Amicone wrote the paper; Aurora Perez Ys, Giuseppe Gatta, Michele Antonio Prencipe, Eleonora Riccio, and Ivana Capuano reviewed all the current literature; Filippo Aucella, Antonio Pisani, and Yuri Battaglia reviewed the paper.

- 20 Wirtz N, Wahl P, Kleinöder H, Mester J. Lactate kinetics during multiple set resistance exercise. *J Sports Sci Med*. 2014;13(1):73–7.
- 21 Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical activity and mortality in chronic kidney disease (NHANES III). *Clin J Am Soc Nephrol*. 2009;4(12):1901–6. <https://doi.org/10.2215/CJN.01970309>
- 22 Parrish AE. The effect of minimal exercise on the blood lactate in azotemic subjects. *Clin Nephrol*. 1981;16(1):35–9.
- 23 Meierhenrich R, Jedicke H, Voigt A, Lange H. The effect of erythropoietin on lactate, pyruvate and excess lactate under physical exercise in dialysis patients. *Clin Nephrol*. 1996;45(2):90–7.
- 24 Clyne N, Esbjörnsson M, Jansson E, Jogestrand T, Lins LE, Pehrsson SK. Effects of renal failure on skeletal muscle. *Nephron*. 1993;63(4):395–9. <https://doi.org/10.1159/000187241>
- 25 Villanego F, Naranjo J, Vigara LA, Cazorla JM, Montero ME, García T, et al. Impact of physical exercise in patients with chronic kidney disease: systematic review and meta-analysis. *Nefrologia*. 2020;40(3):237–52. <https://doi.org/10.1016/j.nefro.2020.01.002>
- 26 Moura SRG, Corrêa HL, Neves RVP, Santos CAR, Neto LSS, Silva VL, et al. Effects of resistance training on hepcidin levels and iron bioavailability in older individuals with end-stage renal disease: a randomized controlled trial. *Exp Gerontol*. 2020;139:111017. <https://doi.org/10.1016/j.exger.2020.111017>
- 27 Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: a potential new treatment for anemia in patients with CKD. *Am J Kidney Dis*. 2017;69(6):815–26. <https://doi.org/10.1053/j.ajkd.2016.12.011>
- 28 Zheng XQ, Lin JL, Huang J, Wu T, Song CL. Targeting aging with the healthy skeletal system: the endocrine role of bone. *Rev Endocr Metab Disord*. 2023;24(4):695–711. <https://doi.org/10.1007/s1154-023-09812-6>
- 29 Russo D, Battaglia Y. Clinical significance of FGF-23 in patients with CKD. *Int J Nephrol*. 2011;2011:364890. <https://doi.org/10.4061/2011/364890>
- 30 Wong L, McMahon LP. Crosstalk between bone and muscle in chronic kidney disease. *Front Endocrinol*. 2023;14:1146868. <https://doi.org/10.3389/fendo.2023.1146868>
- 31 Lombardi G, Ziemann E, Banfi G. Physical activity and bone health: what is the role of immune system? A narrative review of the ThirdWay. *Front Endocrinol*. 2019;10:10–60. <https://doi.org/10.3389/fendo.2019.00060>
- 32 Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol*. 2003;275(2):1081–101. <https://doi.org/10.1002/ar.a.10119>
- 33 Tobeiha M, Moghadasian MH, Amin N, Jafarnejad S. RANKL/RANK/OPG pathway: a mechanism involved in exercise-induced bone remodeling. *BioMed Res Int*. 2020;2020:6910312. <https://doi.org/10.1155/2020/6910312>
- 34 Faienza MF, Lassandro G, Chiarito M, Valente F, Ciaccia L, Giordano P. How physical activity across the lifespan can reduce the impact of bone ageing: a literature review. *Int J Environ Res Public Health*. 2020;17(6):1862. <https://doi.org/10.3390/ijerph17061862>
- 35 Chang X, Xu S, Zhang H. Regulation of bone health through physical exercise: mechanisms and types. *Front Endocrinol*. 2022;13:1029475. <https://doi.org/10.3389/fendo.2022.1029475>
- 36 Aguilar A, Gifre L, Ureña-Torres P, Carrillo-López N, Rodríguez-García M, Massó E, et al. Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis. *Front Physiol*. 2023;14:1177829. <https://doi.org/10.3389/fphys.2023.1177829>
- 37 Malluche HH, Mawad HW, Monier-Faugere M-C. Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res*. 2011;26(6):1368–76. <https://doi.org/10.1002/jbmr.309>
- 38 Bover J, Ureña P, Brandenburg V, Goldsmith D, Ruiz C, DaSilva I, et al. Adynamic bone disease: from bone to vessels in chronic kidney disease. *Semin Nephrol*. 2014;34(6):626–40. <https://doi.org/10.1016/j.semnephrol.2014.09.008>
- 39 Choi RB, Robling AG. The Wnt pathway: an important control mechanism in bone's response to mechanical loading. *Bone*. 2021;153:116087. <https://doi.org/10.1016/j.bone.2021.116087>
- 40 Neves RVP, Corrêa HL, Deus LA, Reis AL, Souza MK, Simões HG, et al. Dynamic not isometric training blunts osteo-renal disease and improves the sclerostin/FGF23/Klotho axis in maintenance hemodialysis patients: a randomized clinical trial. *J Appl Physiol*. 2021;130(2):508–16. <https://doi.org/10.1152/jappphysiol.00416.2020>
- 41 Schiavi SC. Sclerostin and CKD-MBD. *Curr Osteoporos Rep*. 2015;13(3):159–65. <https://doi.org/10.1007/s11914-015-0263-2>
- 42 Marinho SM, Mafra D, Pelletier S, Hage V, Teuma C, Laville M, et al. In hemodialysis patients, intradialytic resistance exercise improves osteoblast function: a pilot study. *J Ren Nutr*. 2016;26(5):341–5. <https://doi.org/10.1053/j.jrn.2016.03.002>
- 43 Gomes TS, Aoike DT, Baria F, Gracioli FG, Moyses RMA, Cuppari L. Effect of aerobic exercise on markers of bone metabolism of overweight and obese patients with chronic kidney disease. *J Ren Nutr*. 2017;27(5):364–71. <https://doi.org/10.1053/j.jrn.2017.04.009>
- 44 Carrillo-López N, Martínez-Arias L, Fernández-Villabrille S, Ruiz-Torres MP, Dusso A, Cannata-Andía JB, et al. Role of the RANK/RANKL/OPG and wnt/β-catenin systems in CKD bone and cardiovascular disorders. *Calcif Tissue Int*. 2021;108(4):439–51. <https://doi.org/10.1007/s00223-020-00803-2>
- 45 Tobeiha M, Moghadasian MH, Amin N, Jafarnejad S. RANKL/RANK/OPG pathway: a mechanism involved in exercise-induced bone remodeling. *BioMed Res Int*. 2020;2020:6910312. <https://doi.org/10.1155/2020/6910312>
- 46 Marinho SM, Eduardo JCC, Mafra D. Effect of a resistance exercise training program on bone markers in hemodialysis patients. *Sci Sport*. 2017;32:99–105.
- 47 Corrêa HL, Neves RVP, Deus LA, Souza MK, Haro AS, Costa F, et al. Blood flow restriction training blunts chronic kidney disease progression in humans. *Med Sci Sports Exerc*. 2021;53(2):249–57. <https://doi.org/10.1249/MSS.0000000000002465>
- 48 Liao HW, Huang TH, Chang YH, Liou HH, Chou YH, Sue YM, et al. Exercise alleviates osteoporosis in rats with mild chronic kidney disease by decreasing sclerostin production. *Int J Mol Sci*. 2019;20(8):2044. <https://doi.org/10.3390/ijms20082044>
- 49 Avin KG, Allen MR, Chen NX, Srinivasan S, O'Neill KD, Troutman AD, et al. Voluntary wheel running has beneficial effects in a rat model of CKD-mineral bone disorder (CKD-MBD). *J Am Soc Nephrol*. 2019;30(10):1898–909. <https://doi.org/10.1681/ASN.2019040349>
- 50 Rosa CSC, Nishimoto DY, Souza GDE, Ramirez AP, Carletti CO, Daibem CGL, et al. Effect of continuous progressive resistance training during hemodialysis on body composition, physical function and quality of life in end-stage renal disease patients: a randomized controlled trial. *Clin Rehabil*. 2018;32(7):899–908. <https://doi.org/10.1177/0269215518760696>
- 51 Marinho SM, Moraes C, Barbosa JE, Carraro Eduardo JC, Fouque D, Pelletier S, et al. Exercise training alters the bone mineral density of hemodialysis patients. *J Strength Cond Res*. 2016;30(10):2918–23. <https://doi.org/10.1519/JSC.0000000000001374>
- 52 Ozawa M, Hirawa N, Haze T, Haruna A, Kawano R, Komiya S, et al. The implication of calf circumference and grip strength in osteoporosis and bone mineral density among hemodialysis patients. *Clin Exp Nephrol*. 2023;27(4):365–73. <https://doi.org/10.1007/s10157-022-02308-8>
- 53 Cardoso DF, Marques EA, Leal DV, Ferreira A, Baker LA, Smith AC, et al. Impact of physical activity and exercise on bone health in patients with chronic kidney disease: a systematic review of observational and experimental studies. *BMC Nephrol*. 2020;21(1):334. <https://doi.org/10.1186/s12882-020-01999-z>
- 54 West SL, Lok CE, Jamal SA. Osteoprotegerin and fractures in men and women with chronic kidney disease. *J Bone Miner Metab*. 2014;32(4):428–33. <https://doi.org/10.1007/s00774-013-0506-1>
- 55 Yoshioka M, Kosaki K, Matsui M, Shibata A, Oka K, Kuro-O M, et al. Replacing sedentary time for physical activity on bone density in patients with chronic kidney disease. *J Bone Miner Metab*. 2021;39(6):1091–100. <https://doi.org/10.1007/s00774-021-01255-w>
- 56 Haarhaus M, Aaltonen L, Cejka D, Cozzolino M, de Jong RT, D'Haese P, et al. Management of fracture risk in CKD: traditional and novel approaches. *Clin Kidney J*. 2023;16(3):456–72. <https://doi.org/10.1093/ckj/sfac230>