Emerging Association Between Parathyroid Hormone and Anemia in Hemodialysis Patients

Motoko Tanaka,1 Hirotaka Komaba2,3, and Masafumi Fukagawa2

1Department of Nephrology, Akebono Clinic, Kumamoto, 2Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine and 3The Institute of Medical Sciences, Tokai University, Isehara, Japan

Abstract: Anemia is a common complication of chronic kidney disease (CKD). There are various causes of renal anemia such as decreased production of erythropoietin, resistance to erythropoietin, shortened survival of red blood cells, and bone marrow fibrosis. Secondary hyperparathyroidism (SHPT) is a less recognized, but potentially significant cause of renal anemia in CKD patients. Parathyroid hormone (PTH) has been regarded as a uremic toxin that has multiple adverse effects, and its elevated levels have been associated with renal anemia in hemodialysis patients. Moreover, recent clinical studies have shown that the treatment of SHPT using either vitamin D receptor activators, calcimimetics, or parathyroidectomy leads to improvement of anemia, supporting the role of PTH in renal anemia. Emerging data have also indicated the involvement of bone-derived fibroblast growth factor 23 in renal anemia. This review summarizes recent insights into the role of PTH in renal anemia and discusses the importance of treating SHPT in improving the control of renal anemia in hemodialysis patients.

Key Words: Anemia, Erythropoietin, Fibroblast growth factor 23, Parathyroid hormone, Secondary hyperparathyroidism.

Anemia is a common complication of chronic kidney disease (CKD) (1). There are various causes of renal anemia such as decreased production of erythropoietin (EPO), resistance to EPO, shortened survival of red blood cells (RBCs), and bone marrow fibrosis. Secondary hyperparathyroidism (SHPT) is a less recognized, but potentially significant cause of renal anemia in CKD patients. Parathyroid hormone (PTH) has been regarded as a uremic toxin that has multiple adverse effects, and its elevated levels have been associated with renal anemia in hemodialysis patients. Moreover, recent clinical studies have shown that the treatment of SHPT using either vitamin D receptor activators (VDRAs), calcimimetics, or parathyroidectomy leads to improvement of anemia. Furthermore, emerging data have indicated the involvement of bone-derived fibroblast growth factor 23 in renal anemia. This review summarizes recent insights into the role of PTH in renal anemia and discusses the importance of treating SHPT in improving the control of renal anemia in hemodialysis patients.

PATHOGENESIS OF RENAL ANEMIA ASSOCIATED WITH SHPT

Bone marrow fibrosis

Studies have provided evidence suggesting that SHPT plays crucial roles in renal anemia, which is mediated via multiple pathways (2). The classical theory was that excess secretion of PTH leads to...
bone marrow fibrosis and consequent interference with erythropoiesis. This possibility was first raised by Rao et al., who demonstrated that patients with a poor response to EPO had higher percentages of osteoclastic and eroded bone surfaces and greater degree of marrow fibrosis in association with higher PTH levels compared to those with a good response (3). This finding indicates that the severity of SHPT and the extent of bone marrow fibrosis increase the dose of EPO needed to achieve an adequate hematocrit response.

**Inhibition of EPO synthesis**

Several studies have also suggested that SHPT affects endogenous EPO synthesis. Although ESRD patients undergoing dialysis have little, if any, kidney function, they may still have preserved function to synthesize EPO. Two independent groups evaluated the effect of surgical PTx, the definitive therapy for refractory SHPT, and consistently demonstrated a significant increase in circulating EPO levels after PTx (4,5). These findings suggest that high PTH levels suppress the endogenous EPO synthesis and thereby contribute to renal anemia, although the molecular mechanisms through which PTH negatively regulates EPO synthesis are mostly unknown.

**Inhibition of bone marrow erythroid progenitors**

An early study by Meytes et al. showed that PTH in concentrations comparable to those found in the blood of uremic patients produces a marked inhibition of mouse bone marrow burst-forming units-erythroid (BFU-E) and increasing the concentration of EPO overcomes this action of PTH (6). However, these results have not been reproduced by other groups (16–18), leaving it unclear whether PTH inhibits erythropoiesis in renal failure.

**Shortened RBC survival**

The effect of PTH on RBC osmotic fragility was examined by Bogin et al. (7). They demonstrated that PTH increases the osmotic fragility of RBC through enhanced calcium entry into RBC. A subsequent study by Akmal et al. further showed that $^{51}$Cr-labeled RBC survival was shortened in 5/6 nephrectomized dogs, but the reduced RBC survival was attenuated and normalized in uremic dogs with parathyroidectomy (8). These data suggest that PTH is among the factors responsible for the shortened RBC survival in renal failure.

**Elevated FGF23 levels**

The principal role of FGF23 is to induce urinary phosphate excretion, suppresses 1,25-dihydroxyvitamin D (1,25[OH]$_2$D) production, and inhibit PTH secretion through binding to the Klotho-FGFR1 complex (9–11). However, accumulating evidence has suggested detrimental effects of FGF23 on non-target organs in a Klotho-independent manner (12). Coe et al. have shown that FGF23 negatively regulates erythropoiesis through suppression of EPO production and EPO receptor expression (13). Furthermore, a recent experimental study by Singh has demonstrated that FGF23 directly targets hepatocytes to promote inflammation (14). Because chronic inflammation is a common cause of anemia, the FGF23-induced inflammation may also contribute to the renal anemia and hyporesponsiveness to EPO. Supporting these experimental findings, a recent report from the Chronic Renal Insufficiency Cohort Study (CRIC) demonstrated significant associations of elevated FGF23 levels with prevalent anemia, change in hemoglobin over time, and development of anemia (15).

**CLINICAL STUDIES LINKING RENAL ANEMIA AND SHPT**

**High PTH levels**

The possible roles of PTH in renal anemia have been supported by a number of clinical observations. Several observational studies have examined the association between PTH levels and renal anemia. Kalantar-Zadeh et al. analyzed the national database of a large dialysis organization and showed that higher PTH levels were independently associated with ESA hyporesponsiveness (19). Similarly, in another cohort of hemodialysis patients, Gaweda et al. reported a modest but significant association between higher PTH levels and decreased erythropoietic response (20).

**Parathyroidectomy**

PTx is the most drastic treatment for SHPT, and early studies have focused on the effect of PTx on EPO doses or hemoglobin levels to explore the role of PTH in renal anemia (21–26). One of the most representative studies was conducted by Trunzo et al. (26). The researchers analyzed data from 37 ESRD patients who underwent PTx for severe SHPT and found that PTx led to a profound decrease in EPO doses with hemoglobin levels being an upward trend. Similar findings have been
reported by multiple independent groups, and these highly consistent results may suggest a substantial beneficial effect of PTx on renal anemia.

**Calcimimetics**

Calcimimetic cinacalcet hydrochloride is the most recent option for the treatment of SHPT (27). This agent allosterically modulates the parathyroid calcium-sensing receptor (CaSR) and increases its sensitivity to extracellular calcium, thereby decreasing PTH synthesis and secretion (28). Since the introduction of cinacalcet, several small-scale studies examined the impact of cinacalcet on renal anemia (29,30). These studies reported an increase in hemoglobin levels or a reduction in the doses of erythropoiesis-stimulating agents (ESA) following the use of cinacalcet for SHPT.

To further validate these preliminary findings, we analyzed data from the MBD-5D, a multicenter, prospective observational study of Japanese hemodialysis patients with SHPT (31). We defined the primary outcome measure as the achievement of a hemoglobin level \( \geq 10.0 \text{ g/dL} \). Among 3201 cinacalcet-naïve individuals at baseline, cinacalcet was initiated in 1337 individuals during the follow up. After adjusting for potential confounders, we found that each additional 6-month duration on cinacalcet was associated with a 1.1-fold increase in the odds of achieving the target hemoglobin level.

There are several possible mechanisms through that cinacalcet could improve renal anemia. The most plausible mechanism is that decreased PTH levels by cinacalcet attenuate the multiple inhibitory effects of PTH on erythropoiesis. In addition, because cinacalcet also inhibits FGF23 secretion (32,33), cinacalcet-induced reduction in FGF23 levels may contribute to improved renal anemia. Furthermore, it should be noted that the CaSR is also expressed in hematopoietic stem cells and has a function in retaining these cells in close physical proximity to the endosteal surface of the bone marrow and the regulatory niche components (34). Thus, it is possible the allosteric action of cinacalcet on CaSR enhances the lodging of hematopoietic stem cells in the endosteal niche and thereby facilitates erythropoiesis.

**Vitamin D**

Treatment with VDRAs, such as calcitriol and maxacalcitol, has long been the primary strategy for the management of SHPT. Several nonrandomized studies examined the effect of VDRAs on renal anemia and demonstrated a reduction in EPO doses or improved hemoglobin levels among patients treated with VDRAs (35–37). The most probable mechanism for the effect of VDRAs is via the decreased PTH levels, but accumulating evidence suggests potential health benefits of vitamin D beyond suppressing PTH secretion. Indeed, several observational studies have shown an independent association between lower 25-hydroxyvitamin D (25 [OH]D) levels and lower hemoglobin concentrations in the CKD population (38,39). In this context, some researchers hypothesize that such pleiotropic effects of vitamin D require the local production of 1,25(OH)\(_2\)D via extrarenal 1α-hydroxylases, and thus nutritional vitamin D can enhance erythropoiesis. To test this hypothesis, Miskulin et al. have recently conducted a randomized clinical trial in hemodialysis patients with vitamin D insufficiency or deficiency (40). The investigators demonstrated that 6 months of supplementation with ergocalciferol increased serum 25(OH)D levels, but had no effect on EPO dose. These findings indicate that nutritional vitamin D has no role to play in the management of anemia in hemodialysis patients. It remains, however, unknown whether systemically administered VDRAs directly affect erythropoiesis independently of the effect on PTH. Further research is required to evaluate this possibility.

**CONCLUSIONS**

This review summarizes recent experimental and clinical data suggesting the role of PTH in renal anemia. Accumulating evidence supports the causal role of PTH in renal anemia and provide additional rationale for controlling PTH secretion in ESRD patients. Future clinical trials should determine the effect of PTH-lowering therapy on hemoglobin levels or ESA doses as a primary endpoint.

**Acknowledgment:** The article processing charge for this proceeding was paid for by Ono Pharmaceutical, as part of an unrestricted educational grant.

**Conflict of Interest:** HK has received honoraria, consulting fees, and/or grant/research support from Bayer Yakuhin, Chugai Pharmaceutical, Kyowa Hakko Kirin, and Ono Pharmaceutical. MF has received honoraria, consulting fees, and/or grant/research support from Astellas Pharma, Bayer Yakuhin, EA Pharma, Kyowa Hakko Kirin, Ono Pharmaceutical, and Torii Pharmaceutical. The remaining author has no conflicts of interest.

© 2018 The Authors. Therapeutic Apheresis and Dialysis published by John Wiley & Sons Australia, Ltd on behalf of International Society for Apheresis, Japanese Society for Apheresis, and Japanese Society for Dialysis Therapy
REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012;23:1631–4.
2. Brancaccio D, Cozzolino M, Gallieni M. Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. J Am Soc Nephrol 2004;15 (Suppl 1):S21–4.
3. Rao DS, Shih MS, Mohini R. Effect of serum parathyroid hormone and bone marrow fibrosis on the response to erythropoietin in uremia. N Engl J Med 1993;328:171–5.
4. Urena P, Eckardt KU, Sarfati E et al. Serum erythropoietin and erythropoiesis in primary and secondary hyperparathyroidism: effect of parathyroidectomy. Nephron 1991;59:384–93.
5. Washio M, Iseki K, Onayoma K et al. Elevation of serum parathyroid hormone in patients with chronic renal failure. Intern Med 1992;31:627–30.
6. Meytes D, Belin E, Ma A, Dukes PP, Masry SG. The effect of parathyroid hormone on erythropoiesis. J Clin Invest 1981;67:1263–9.
7. Bogin E, Massry SG, Levi J, Djaldetti M, Bristol G, Smith J. Effect of parathyroid hormone on osmotic fragility of human erythrocytes. J Clin Invest 1982;69:1017–25.
8. Akmal M, Telfer N, Ansari AN, Massry SG. Erythrocyte survival in chronic renal failure. Role of secondary hyperparathyroidism. J Clin Invest 1985;76:1695–8.
9. Shimada T, Mizutani S, Muto T et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A 2001;98:6500–5.
10. Urakawa I, Yamazaki Y, Shimada T et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006;444:770–4.
11. Komaba H, Fukagawa M. Cinacalcet and clinical outcomes in dialysis. Semin Dial 2015;28:594–603.
12. Block GA, Martin KJ, de Francisco AL et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 2004;350:1516–25.
13. Battistella M, Richardson RMA, Bargman JM, Chan CT. Improved parathyroid hormone control by cinacalcet is associated with reduction in darbepoetin requirement in patients with end-stage renal disease. Clin Nephrol 2011;76:99–103.
14. Mpio I, Boumendjel N, Karaslan H et al. Secondary hyperparathyroidism and anemia. Effects of a calcimimetic on the control of anemia in chronic hemodialysed patients. Pilot Study. Nephrol Ther 2011;7:229–36.
15. Tanaka M, Yoshida K, Fukuma S et al. Effects of secondary hyperparathyroidism treatment on improvement in anemia: results from the MBD-5D study. PLoS One 2016;11:e0164865.
16. Koizumi M, Komaba H, Nakashima S, Fujimori A, Fukagawa M. Cinacalcet treatment and serum FGF23 levels in haemodialysis patients with secondary hyperparathyroidism. Nephrol Dial Transplant 2012;27:784–90.
17. Moe SM, Chertow GM, Parfrey PS et al. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the evaluation of cinacalcet HCl therapy to lower parathyroid hormone (E VOLVE) trial. Circulation 2015;132:27–39.
18. Adams GB, Chabner KT, Alley IR et al. Stem cell engrafment at the endosteal niche is specified by the calcium-sensing receptor. Nature 2006;449:599–603.
19. Albitar S, Genin R, Fen-Chong M, Serveaux MO, Schohn D, Chuet C. High-dose alfalcaldiol improves anaemia in patients on haemodialysis. Nephrol Dial Transplant 1997;12:514–8.
20. Goicoechea M, Vazquez MI, Ruiz MA, Gomez-Campfreda P, Perez-Garcia R, Valderrubarto F. Intravenous calcitriol improves anaemia and reduces the need for erythropoietin in haemodialysis patients. Nephron 1998;78:23–7.
21. Aceula F, Scalzulli RP, Gatta G, Vigilante M, Carella AM, Scalzulli RP. Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure. A synergistic effect with r-HuEpo. Nephron Clin Pract 2003;95:121–7.
22. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency and inflammation and their association with hemoglobin levels in chronic kidney disease. Am J Nephrol 2009;30:64–72.
23. Patel NM, Gutierrez OM, Andress DL, Coyne DW, Levin A, Wolf M. Vitamin D deficiency and anaemia in early chronic kidney disease. Kidney Int 2010;77:715–20.
24. Miskulin D, Majchrzak K, Tighiouart H et al. Ergocalciferol supplementation in hemodialysis patients with vitamin D deficiency: a randomized clinical trial. J Am Soc Nephrol 2015;27:1801–10.