



## Secondary Hyperparathyroidism in chronic kidney disease patients; current knowledge

Masoud Amiri<sup>1</sup>, Hamid Nasri<sup>2\*</sup>

When renal function diminishes, secondary hyperparathyroidism with develop in response to worsening of kidney function and declined phosphate excretion (1). Dysregulation of phosphorous and calcium homeostasis leads to decreased kidney phosphate excretion, raised serum phosphorous, reduced synthesis of calcitriol, and elevated levels of the phosphatonin fibroblast growth factor 23 (FGF-23) (2-4). These alterations result in parathyroid hyperplasia and enhanced synthesis and secretion of parathyroid hormone participating to the development of a vicious cycle (3-5). Hence, continuous stimulus of the parathyroid glands by a mixture of decreased extracellular ionized calcium concentration, elevated extracellular phosphate concentration, and significantly reduced serum calcitriol leads to increased parathormone synthesis and release (3-7). Together, elevated FGF-23 expression down-regulates residual kidney 25(OH)-1-hydroxylase, which aggravates the deficiency of calcitriol, working as an additional handler to hyperparathyroidism. Even at early phases in the development of hyperparathyroidism, these modifications are compounded by variable under-expression of the calcium-sensing receptor and vitamin D receptor, giving the parathyroid cells incapable to react appropriately to ambient calcium and/or calcitriol. The ensuing increase in proliferative activity in the parathyroid glands finally leads to parathyroid hyperplasia (2-6). Current knowledge of the molecular mechanisms following phosphorous homeostasis has shown FGF-23 and its receptor fibroblast growth factor receptor 1 (FGFR1) have important role. FGF-23 is a hormone which its production in the osteocytes and osteoblasts is provoked by phosphate increment and calcitriol raise. FGF-23 binds to and activates FGFR1, which is functional merely if co-expressed with the Klotho transmembrane protein, as a Klotho-FGF receptor complex. It was found that, in the proximal tubule, FGF-23 diminishes phosphate reabsorption by moderating the expression of type II sodium phosphate co-transporters (3-7). Hence, rises in both serum FGF-23 and parathormone in patients

### ■ Implication for health policy/practice/research/medical education

Secondary hyperparathyroidism is a progressive disease common in patients with chronic renal failure and with serious concerns for patient health. If unsuccessfully controlled, secondary hyperparathyroidism develops and can lead to soft tissue calcification, bone disease, and vascular calcification, which adversely impact mortality and morbidity. Conventional therapies that target vitamin D and phosphorous levels are not without disadvantages. The appearance of the calcimimetics and a better understanding of the strengths and limitations of native and active vitamin D compounds have advanced the treatment options for patients with secondary hyperparathyroidism.

with chronic renal failure decrease the proximal tubular reabsorption of phosphate and keep normo-phosphatemia in most patients till the glomerular filtration rate decreases below 20 ml/min. Predictably, as chronic renal failure progresses, these negative feedback loops are progressively disrupted and finally unable to keep phosphate homeostasis (4-9). FGF-23 also reduces parathormone synthesis directly, while indirectly enhancing synthesis via reduction of kidney calcitriol fabrication. Correlations between high FGF-23 level in patients on dialysis, refractory secondary hyperparathyroidism, and increased mortality have been detected. On the other hand, high phosphate increases parathyroid hyperplasia. While, there was no confirmation to propose the presence of a phosphorous receptor on the parathyroid gland, various studies propose that vitamin D pathways play a secondary task in the development of parathyroid gland hyperplasia and that signaling across the calcium-sensing receptor is enough to prevent parathyroid hyperplasia. Patients in the early phases of chronic renal failure do not frequently present any changes in their serum phosphate and calcium levels (7-10). However, their parathormone levels may be only marginally higher than normal values. Various new

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<sup>1</sup>Social Health Determinants Research Center, Shahrekord University of Medical Sciences Shahrekord, Iran. <sup>2</sup>Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran.

\*Corresponding author: Prof. Hamid Nasri, E-mail: hamidnasri@med.mui.ac.ir

publications have described raised levels of FGF-23 in chronic renal failure patients, which may help to control serum levels of phosphate and calcium. The provocations for secretion of FGF-23 in early chronic renal failure are not completely found, and this is under investigation (6-11). FGF-23 does not seem to be an acute postprandial regulator of phosphaturia in chronic renal failure, however inappropriate postprandial hypocalcemia could represent a previously unreported mechanism of secondary hyperparathyroidism in chronic renal failure. Studies on the effect of FGF-23 on parathyroid function in normal and hyperplastic parathyroid glands revealed that FGF-23 diminished parathormone secretion and cell proliferation and increased calcium-sensing receptor and vitamin D receptor expression in normal glands (2-6,9-12). On the contrary, FGF-23 did not have an effect on hyperplastic glands. Thus, secondary hyperparathyroidism is a progressive disease common in patients with chronic renal failure and with serious concerns for patient health. If unsuccessfully controlled, secondary hyperparathyroidism develops and can lead to soft tissue calcification, bone disease, and vascular calcification, which adversely impact mortality and morbidity (10-15). Conventional therapies that target vitamin D and phosphorous levels are not without disadvantages. The appearance of the calcimimetics and a better understanding of the strengths and limitations of native and active vitamin D compounds have advanced the treatment options for patients with secondary hyperparathyroidism (12-15).

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All authors wrote the paper equally.

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