REVIEW ARTICLE

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Phosphate balance in chronic kidney disease: the chicken or the egg?

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ABSTRACT

In chronic kidney disease patients there are three main stimuli for parathyroid hormone (PTH) secretion by the chief cell in the parathyroid glands: hypocalcaemia, low $1,25(OH)_2D_3$ levels and hyperphosphataemia.

FGF23 is a regulator of phosphate and vitamin D metabolism. The discovery of FGF23 actions enlightened our understanding of the development of secondary hyperparathyroidism in CKD patients. The main systemic factors that stimulate FGF23 secretion by the osteocyte in the bone appear to be phosphate load and $1,25(OH)_2D_3$. In the kidney, FGF23 decreases the number of Na/Pi co-transporters IIa and IIc in the tubular cell and promotes phosphaturia. FGF23 also reduces $1,25(OH)_2D_3$ levels by inhibiting, in the kidney, its production by 1-alpha-hydroxylase and stimulating its degradation by 24-hydroxylase. Increase in FGF23 levels has been described in early 2 and 3 CKD stages preceding the decrease of $1,25(OH)_2D_3$ levels and hyperphosphatemia. In this sequence of events, increase of FGF23 in CKD patients seems to be a novel mechanism for the early decline of $1,25(OH)_2D_3$ levels observed in these patients. It was hypothesised that klotho deficiency creates a tissue resistance to FGF23 which is responsible for the increase of FGF23 levels. Reduced renal expression of klotho has been demonstrated in CKD patients preceding FGF23 increase. Chronic kidney disease may be considered a state of klotho deficiency with increase of FGF23 levels. Klotho deficiency may be the initial alteration for the development of phosphate retention and secondary hyperparathyroidism in CKD patients. In this article we review the classic and new pathways involved in the development of secondary hyperparathyroidism in chronic kidney disease and the subsequent actions ensuing from this knowledge. It is possible that, in 3 and 4 CKD stages, an early therapeutic intervention consisting of a low phosphate diet and/or phosphate binders, even in the presence of normophosphataemia, might retard the development of secondary hyperparathyroidism.

Key-Words:
Bone-kidney-parathyroid endocrine axis; chronic kidney disease; FGF 23; Klotho; phosphate balance.

STIMULI FOR PARATHYROID HORMONE SYNTHESIS AND SECRETION WITH THE CONSEQUENT DEVELOPMENT OF SECONDARY HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE

In chronic kidney disease (CKD) patients there are three main stimuli for parathyroid hormone (PTH) secretion by the chief cell in the parathyroid glands: hypocalcaemia, low $1,25(OH)_2D_3$ levels and hyperphosphataemia[1] (Fig.1). Low $1,25(OH)_2D_3$ levels and low calcium levels directly stimulate the parathyroid cell through their action on specific receptors, the vitamin D receptor[2] in the nucleus and the calcium

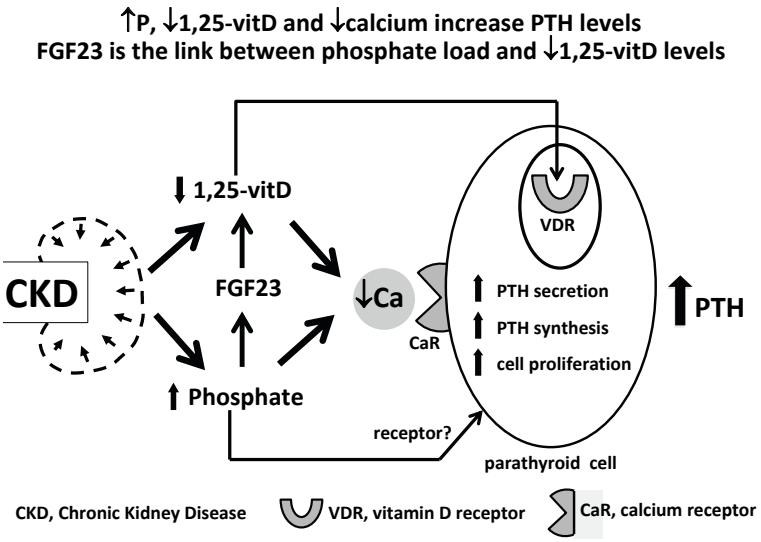

Figure 1

Development of secondary hyperparathyroidism in CKD

receptor[3] in the cell membrane, respectively. A receptor for phosphate has not yet been identified in the parathyroid cell, but a direct effect of hyperphosphataemia on PTH secretion, independent of its effect on calcium and $1,25(OH)_2D_3$, has already been demonstrated[4-6]; $1,25(OH)_2D_3$ decreases PTH gene transcription[7] and calcium and phosphate regulate the PTH gene post-transcriptionally[8].

In the normal parathyroid gland few cells proliferate. In secondary hyperparathyroidism there is an increase in parathyroid cell number, in PTH gene expression and secretion. Hypocalcaemia, hyperphosphataemia and uraemia lead to parathyroid cell proliferation[9].

CALCIUM, PHOSPHATE AND $1,25(OH)_2D_3$ LEVELS DURING CKD PROGRESSION

1. Hyperphosphataemia contributes to the development of secondary hyperparathyroidism

The trade-off hypothesis has conferred on phosphate a pivotal role in the development of secondary hyperparathyroidism[10] and hyperphosphataemia has been considered the primordial stimulus for the development of this pathological condition[11]. The observation that hyperphosphataemia is only present in late 4 and 5 CKD stages[12,13] has cast doubts on phosphate's alleged role in stimulating PTH secretion in early CKD stages. However, this imaginative hypothesis holds true when applied to more advanced CKD stages. The mechanisms commonly considered as explaining the development of hyperparathyroidism in consequence of hyperphosphataemia are the phosphorus-induced decrease in $1,25(OH)_2D_3$ levels, the phosphorus-induced hypocalcaemia and the direct independent effect of phosphorus on parathyroid cell function[11].

2. $1,25(OH)_2D_3$ deficiency contributes to the development of secondary hyperparathyroidism

The hypothesis that vitamin D plays the primordial role in the progression of secondary hyperparathyroidism has also been raised[14]. This hypothesis has been strengthened by more recent studies demonstrating that reductions of $1,25(OH)_2D_3$ levels appear in early CKD stages and precede the development of hyperphosphataemia[15,16].

3. Hypocalcaemia contributes to the development of secondary hyperparathyroidism

The development of hypocalcaemia is an event that occurs in late CKD stages[12,13] and has been explained by several factors, such as the lower renal tubular reabsorption from the failing kidney, the lower intestinal absorption of calcium in relation with low $1,25(OH)_2D_3$ levels and the lower release of Ca from bone in relation to hyperphosphataemia[17]. Inappropriate postprandial calciuria with episodic relative hypocalcaemia and increase in PTH levels in 3 and 4 CKD stages is a new proposed mechanism for the development of secondary hyperparathyroidism driven by hypocalcaemia in early CKD stages[18].

FIBROBLAST GROWTH FACTOR 23

Fibroblast growth factors family members are now defined as humoral factors which have in common a three-dimensional β-trefoil structure. To date, twenty-two human fibroblast growth factors have been identified (1 to 14 and 16 to 23) and grouped into seven subfamilies. Fibroblast growth factor (FGF) 23 was identified as the last member of the FGF superfamily and belongs to the FGF19 subfamily.

FGFs execute their biological action by binding to an FGF receptor (FGFR) with an extracellular domain, a single-pass transmembrane domain and an intracellular domain responsible for a tyrosine kinase activity[19]. Contrary to the other FGFs which act in a paracrine way, FGF19 subfamily members achieve their activities in an endocrine fashion. In paracrine FGFs, stable FGF-FGFR binding is regulated by heparin and heparan sulphate[20]. In the FGF19 subfamily heparin or heparan sulphate have a poor ability to promote binding to FGFR, and FGF19 subfamily members require the presence of Klotho or beta-Klotho in their target tissues[21]. Membrane Klotho forms a complex with FGFR and functions as an obligate co-receptor for FGF23[21]. The restricted tissular expression of Klotho proteins also contributes to the endocrine behavior of this subfamily by limiting the signalling of these ligands to the specific tissues[21]. Membrane Klotho has been identified in kidney, in choroid plexus in brain and in parathyroid glands.

The FGFs are now considered to play substantial roles in development, angiogenesis, haematopoiesis and tumorigenesis. FGF19 subfamily members regulate diverse physiological processes uncommon to classical FGFs[21], namely bile acid homeostasis (FGF19), glucose and lipid metabolism (FGF21) and phosphate and vitamin D homeostasis (FGF23).

FGF23 AND THE BONE-KIDNEY-PARATHYROID ENDOCRINE AXIS: A LINK BETWEEN PHOSPHATE LOAD AND LOW VITAMIN D LEVELS

FGF23 is a regulator of phosphate and vitamin D metabolism. It is a 32-kDa protein with 251 amino acids that is secreted mainly by osteocytes in bone[22]. The discovery of FGF23 actions enlightened our understanding of the development of secondary hyperparathyroidism in CKD patients. The main systemic factors that stimulate FGF23 secretion by the osteocyte in the bone appear to be phosphate load[23] and $1,25(OH)_2D_3$[24]. In the kidney, FGF23 decreases the number of Na/Pi co-transporters IIa and IIc in the tubular cell and promotes phosphaturia[25,26]. FGF23 also reduces $1,25(OH)_2D_3$ levels by inhibiting, in the kidney, its production by 1-alpha-hydroxylase[25,26] and stimulating its degradation by 24-hydroxylase[26]. In parathyroid glands, FGF23 suppresses production and secretion of PTH. Suppression of PTH contributes to the reduction of $1,25(OH)_2D_3$ levels. Klotho is much more abundant in distal convoluted tubules than in proximal tubules. It is not known whether FGF23 acts directly or indirectly in the proximal tubule, promoting phosphaturia and inhibiting $1,25(OH)_2D_3$[27].

Increase in FGF23 levels has been described in early 2 and 3 CKD stages[28-30] preceding the decrease of $1,25(OH)_2D_3$ levels and hyperphosphataemia[30,31]. In this sequence of events, increase of FGF23 in CKD patients seems to be a novel mechanism for the early decline of $1,25(OH)_2D_3$ levels observed in these patients[32]. Increased phosphate load stimulates the synthesis of FGF23[25] and FGF23 promotes phosphaturia and maintains phosphate levels between normal ranges. The price to maintain normal phosphate levels is the decrease in $1,25(OH)_2D_3$ levels with the subsequent stimulation of PTH synthesis. In this new

paradigm FGF23 is a determinant player in the pathophysiology of secondary hyperparathyroidism in early CKD stages[32].

FGF23, PHOSPHATE LOAD AND PHOSPHATE RESTRICTION

Phosphate loading in mice increases FGF23 levels[25], but the data in humans are conflicting. Hyperphosphataemia induced by intravenous phosphorus infusion was not associated with increase in FGF23 levels[33]. After an oral phosphate load, an increase in the fractional excretion of phosphate was observed in early CKD patients[18] and healthy volunteers[34] but FGF23 levels did not increase immediately after the oral phosphate load. However, 8 hours after phosphate ingestion, a 20% increase of FGF23 levels was observed in healthy volunteers[34]. The mechanism by which phosphate regulates FGF23 production is still unknown. A phosphate sensor that controls FGF23 production has not been identified and extracellular phosphate has not been shown to regulate FGF23 gene transcription in osteoblast cultures[24], raising the possibility that phosphate effects on FGF23 production might be indirect[35].

In theory, a low phosphate diet and/or the administration of phosphate binders in CKD stages3 and 4, even with normophosphataemia, may prevent the development of mineral abnormalities associated with secondary hyperparathyroidism[36]. Some of the beneficial effects of phosphate restriction in early CKD stages were described more than 25 years ago[37,38]. It was found that a restriction in the dietary intake of phosphorus in patients with moderate renal insufficiency was associated with a decrease in fractional excretion of phosphate[37], increase in $1,25(OH)_2D_3$ levels[37,38] and a decrease in iPTH levels[37,38]. These findings, due to the recent discovery of FGF23 actions, may now be interpreted in a new light.

The effect of phosphate binders in preventing gastrointestinal phosphate absorption and phosphate load has been evaluated in two pilot studies in normophosphataemic CKD stages 3 and 4 patients[39,40]. During a 6-wk period followed by a 2-wk washout period, calcium acetate and sevelamer treatment were associated with a decrease in PTH levels and urinary phosphate; in the sevelamer group but not in the calcium acetate group there was also a decrease in FGF23 levels after the 4^{th} week of treatment[39]. This latter observation of a different effect of calcium acetate and sevelamer on FGF 23 levels still is not fully understandable in the light of present knowledge, but some authors suggest that might be the consequence of a direct effect of calcium load on osteocytes. This study raises the interesting possibility of controlling the mineral metabolism disturbances and secondary hyperparathyroidism with the early control of phosphate loading.

In a very short study with only a 2-wk duration[40], lanthanum carbonate and dietary phosphate restriction lowered urinary phosphate excretion without lowering FGF23.

These interesting preliminary results need to be confirmed in appropriate clinical trials.

The source of protein has also a different effect on phosphorus homeostasis[36]. The diurnal variation of phosphate levels, fractional excretion of phosphate and iPTH levels were consistently lower in a vegetarian diet than a meat diet with similar protein and phosphate content[36]. The source of phosphate should, therefore, be included in the dietary counselling for CKD patients.

FGF23 AND CLINICAL OUTCOMES

FGF23 is a more robust predictor of adverse outcomes in CKD patients than serum phosphate levels[31]. Increased levels of FGF23 have been associated with mortality in incident[41] and prevalent[42] haemodialysis patients and in patients with stable coronary disease, without end-stage renal disease[43]. Increased risk of cardiovascular events has been also predicted by high FGF23 levels in CKD patients not on dialysis[44]. FGF23 increase has been associated with left ventricular hypertrophy[45], left ventricular mass, severe vascular calcification[46] and with increased risk of CKD progression[47]. However, all these observational studies can only demonstrate an association effect between high FGF23 levels and adverse clinical outcomes, and another type of evidence, such as randomised clinical trials, is needed to demonstrate

that high FGF23 levels are the cause of these adverse outcomes.

Another intriguing aspect of the possible causal relationship between FGF23 and cardiovascular events is the fact that although klotho is needed as a co-factor for FGF23 klotho is not expressed in the cardiovascular system, and there is a klotho deficiency in CKD patients[48]. It was hypothesised that very high FGF23 levels, independent of klotho collaboration, may activate other FGF receptors[31] but klotho deficiency also contributes directly to vascular calcification[48]. A recent study has definitely demonstrated a direct contribution of FGF23, independent of klotho, in the development of left ventricular hypertrophy in mice[49].

KLOTHO, PHOSPHATE AND FGF23

Animal models lacking klotho or FGF23 develop similar phenotypes with growth retardation, shortened life span, phosphate retention, osteopaenia and vascular and ectopic calcifications, among other alterations, revealing an unexpected link between phosphate and aging[50,51]. These similar phenotypes of klotho and FGF23 knockout mice have been explained by the discovery that FGF23 requires klotho to bind with high affinity to the FGF receptor[21]. However, in CKD patients, it is the increase of FGF23 levels and not FGF23 level decrease that is associated with mortality, higher risk of cardiovascular events and vascular calcifications[41-47]. This discrepancy with the FGF23 knockout phenotype may be explained by the finding that mice lacking klotho show, similarly, high levels of FGF23[52] (Table I). It was hypothesised that klotho deficiency creates a tissue resistance to FGF23 which is responsible for the increase of FGF23 levels[52]. Reduced renal expression of klotho has been demonstrated in CKD patients[53] preceding FGF23 increase[54]. Chronic kidney disease may be considered a state of klotho deficiency with increase of FGF23 levels similar to what is observed in klotho-deficient mice. The rescue of klotho-deficient or FGF23-deficient mice has been performed by correcting the hyperphosphataemia or hypervitaminosis D with dietary or genetic interventions. These mice do not develop vascular calcifications and show an increase in life span. All these interventions have in common the reduction of phosphate levels, with opposite effects on Ca and vitamin D levels, suggesting that phosphate is primarily responsible for these aging-like phenotypes[54]. Klotho deficiency may be the initial alteration for the development of phosphate retention and secondary hyperparathyroidism in CKD patients[54].

Table I

CKD shares some manifestations of Klotho knockout and FGF23 knockout models

	Klotho KO models	FGF23 KO models	CKD patients
Klotho expression	↓↓↓	normal	↓
FGF23 levels	↑↑↑	↓↓↓	↑↑↑
premature death	yes	yes	yes
vascular calcifications	yes	yes	yes
P levels	↑	↑	↑
Ca levels	↑	↑	↓
1,25-vitD levels	↑	↑	↓

PROPOSED ROLE OF KLOTHO AND FGF23 IN THE DEVELOPMENT OF SECONDARY HYPERPARATHYROIDISM IN CKD (Fig. 2)

Phosphate load in the diet transitorily stimulates FGF23[23,25] with a consequent and adequate phosphaturic action[25,26], contributing to the maintenance of normal phosphate blood levels. In CKD patients, with reduction of renal mass, there is a decrease in the renal expression of klotho[53], contributing to the increased levels of FGF23[52]. In initial CKD stages, this increase of FGF23 levels maintains an efficient phosphate excretion and is associated with an increase of fractional excretion of phosphate and with normal phosphate levels. At the same time FGF23 decreases $1,25(OH)_2D_3$[25,26] by decreasing its synthesis and increasing its catabolism. The decrease of $1,25(OH)_2D_3$ is a stimulus for the increase in the synthesis of PTH[7]. As the kidney insufficiency progresses there is a greater decrease of renal klotho expression to which $1,25(OH)_2D_3$ also deficiency contributes. This decrease in klotho expression contributes to a further increase in FGF23 levels. At this stage, with important reduction of renal mass, FGF23 increase is no longer efficient, and reduced phosphaturia is responsible for the appearance of hyperphosphataemia.

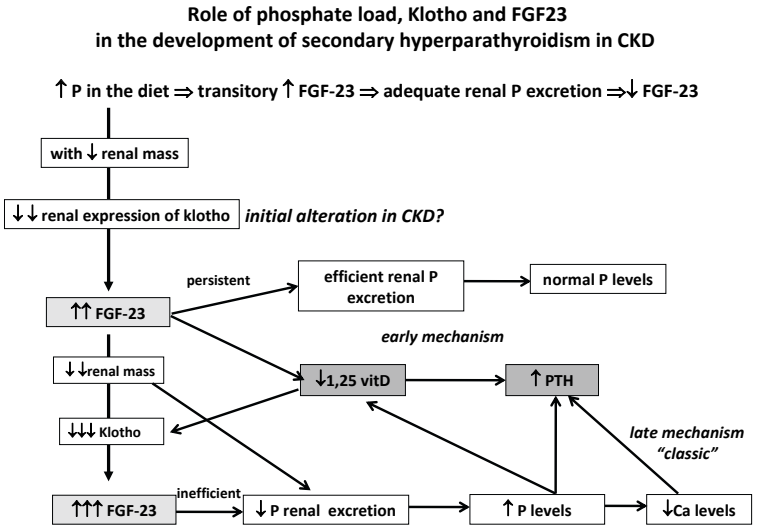

Figure 2

Role of phosphate load, klotho and FGF23 in the development of secondary hyperparathyroidism in CKD

In this proposed pathway for the development of secondary hyperparathyroidism two main mechanisms are recognised: an early mechanism resulting from the increase of FGF23, associated with low $1,25(OH)_2D_3$ levels[32] and a late mechanism, corresponding to the classic trade-off hypothesis derived from hyperphosphataemia. The decrease in the renal expression of klotho precedes the increase of FGF23 levels[54] and may be the initial alteration in CKD patients responsible for the development of secondary hyperparathyroidism[54].

CONCLUSIONS

FGF23 is a regulator of phosphate and vitamin D metabolism. FGF23 levels are increased in early CKD stages. Increase of FGF23 seems to be a novel mechanism for the early decline of $1,25(OH)_2D_3$ levels observed in CKD patients. Phosphate is one of the recogniaed stimuli for FGF23 secretion. In this new updated model for secondary hyperparathyroidism, FGF23 may act as a link between phosphate load and low vitamin D levels [Figs 1 and 2]. The discovery of klotho and FGF23 actions has given back to phosphate a primordial role in the development of secondary hyperparathyroidism.

It is possible that in CKD stages3 and 4 an early therapeutic intervention on phosphate with a low phosphate diet and/or phosphate binders, even in the presence of normophosphataemia[36], might retard the development of secondary hyperparathyroidism.

Conflict of interest statement. None declared.

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Hyperphosphatemia, low 1,25 vit D levels and hypocalcemia are well-known stimuli for development of hyperparathyroidism in CKD patients.

Increase in FGF23 levels is the link between phosphate load and low 1,25 Vit D levels.

The understanding of klotho and FGF23 actions has given back to phosphate a pivotal role in the development of secondary hyperparathyroidism.

In early CKD stages, it is possible that a low phosphate diet and/or phosphate binders, even in the presence of normophosphataemia, might retard the development of secondary hyperparathyroidism.