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Review Article

Treatment of phosphate retention: The earlier the better?

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Abstract

Over the last 15 years, our knowledge and understanding of the underlying mechanisms involved in the regulation of calcium and phosphate homeostasis in chronic kidney disease have advanced dramatically. Contrary to general opinion in the 20th century that moderate hypercalcemia and hyperphosphatemia were acceptable in treating secondary hyperparathyroidism, the calcium and phosphate load is increasingly perceived to be a major trigger of vascular and soft tissue calcification. The current treatment options are discussed in view of historical developments and the expectations of the foreseeable future, focusing on the early treatment of hyperphosphatemia. At present, we lack indisputable evidence that active intervention using currently available drugs is of benefit to patients in chronic kidney disease stages 3 and 4.

Introduction

Renal insufficiency and failure are characterized by multiple and complex disturbances in mineral and bone metabolism. In the past decade, the term chronic kidney disease–mineral and bone disorder (CKD-MBD) was developed to describe a "syndrome" which is not exclusively restricted to bone metabolism. In this context, Block et al [1] showed the relevance of increased serum phosphate levels $\geq$ 5.52 mg/dL (1.78 mmol/L). In 1998, in a large retrospective observational study of hemodialysis patients, such a level of hyperphosphatemia was shown to be associated with a significant increase in death from cardiovascular disease [1]. Later, at the turn of the millennium, an intensive discussion started after the introduction of oral phosphate binders which were not based on calcium regarding the adverse potential of calcium loading of the body as a synergistic trigger of morbidity from cardiovascular disease [2–4]. Since then, both the stigmata of CKD-MBD, hyperphosphatemia and a positive calcium balance, have been accepted as key inductors of the initiation and progression of cardiovascular calcification in CKD.

Historical background

Mortality increases in the early stages of CKD at a creatinine clearance $\leq$ 60 mL/min [5,6]. As we have learnt that vessel calcification is not just a simple passive process of calcium–phosphate precipitation, but is a consequence of modified gene expression with the active induction of phenotype transformation of smooth muscle cells into osteoblasts within the vessel wall [7,8], attention on this process has increased and concentrated on the basic control and regulatory mechanisms involved [9,10]. The aim of this research is to reduce the potentially lethal sequelae of disturbed homeostasis in mineral metabolism in CKD [11]. Multiple and recent epidemiological studies have documented associations between ionic and humoral abnormalities on the one side, and morbidity and mortality on the other [12].

It was initially believed that progressive fibrosis of the kidneys with a loss of normal parenchymal tissue was the functional cause of decreasing excretory function (recognizable by reduced urine production and solute clearance). It was also believed that this was the underlying cause of the progressive decrease in incretory capacity which results in reduced levels of endogenous active vitamin D and compensatory increases in parathyroid hormone (PTH) levels to ward off imminent hypocalcemia (Fig. 1).

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In addition, following the discovery of highly potent, protective hormonal mechanisms which induce an increase in phosphaturia (the so-called phosphatonins) and which thus attenuate the development of hyperphosphatemia, the original concept of an exclusive vitamin D–hypocalcemia perception in the development of CKD-MBD has been modified over the last decade to include a primarily phosphate regulated and regulating paradigm (Fig. 2) [13].

Recently, the COSMOS (Current Management Of Secondary Hyperparathyroidism – a Multicenter Observational Study) study results showed a 22% reduction in all-cause mortality and a 29% reduction in cardiovascular mortality in patients treated with phosphate binders. The open cohort, observational study consisted of 6,797 patients followed prospectively for 3 years in 227 dialysis centers from 20 European countries. Remarkably, the reduction in mortality was also shown in patients treated with calcium-based phosphate binders, whereas more marked reductions were noted in patients treated with combinations of phosphate binders [14].

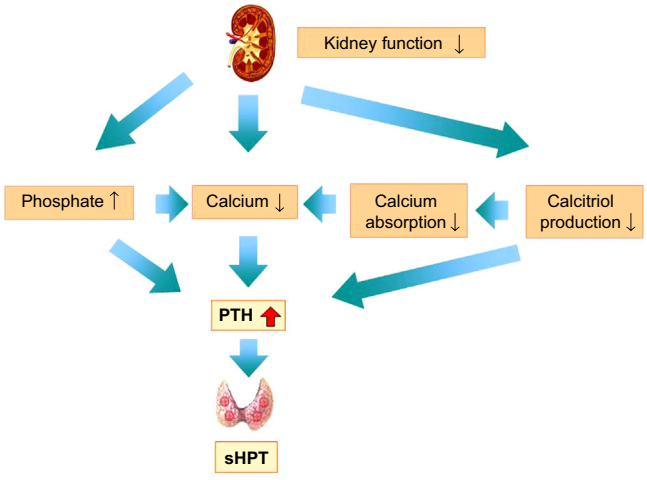

Figure 1. Classic interpretation of secondary hyperparathyroidism due to loss of renal parenchyma and function. PTH, parathyroid hormone; sHPT, secondary hyperparathyroidism. *Note.* From "CME sHPT: Pathophysiologie des sekundären Hyperparathyreoidismus", by Floege and Ketteler, Copyright 2005, *Thieme*, [in German]. Adapted with permission.

Phosphate control mechanisms

The discovery of the phosphatonins, including fibroblast growth factor 23 (FGF-23) [15,16] and Klotho [17] allowed new insights into the pathogenesis of CKD-MBD. FGF-23 consists of 251 amino acids with a molecular weight of 26,000 Da and is produced primarily in osteocytes [18]. As yet, the exact mechanisms which result in its secretion have not been completely elucidated; however, it is generally accepted that increased phosphate loading or hyperphosphatemia directly or indirectly stimulates FGF-23. In addition, calcitriol stimulates the secretion of FGF-23, and FGF-23 is bound into feedback loops which also suppress the secretion of PTH and calcitriol [19–21].

FGF-23 can be detected via its intact and C-terminal sequences, although, at present, certain differential diagnosis cannot be deduced from the two assay targets. Remarkably, FGF-23 values can increase by a factor of more than 1,000-fold in end-stage renal disease, which can, at least in part, be interpreted as a weakening of the feedback loops and, in the case of C-terminal assays, as cumulation in CKD. The production and sensitivity of the receptor-coactivator Klotho is downregulated in CKD as it is also under the direct negative influence of FGF-23. Furthermore, Klotho expression is partially dependent on calcitriol, which is progressively reduced in CKD [22,23].

In the presence of Klotho, FGF-23 binds to FGF receptors, utilizing a dimeric receptor complex to induce specific signal transduction. FGF receptors are detectable in most organs; however, the coexpression of Klotho is specific to the kidneys and parathyroid glands [24].

FGF-23 suppresses the expression of the sodium–phosphate (NaPi) cotransporters NaPi-2a and NaPi-2c in the proximal renal tubules and augments phosphate excretion [25,26]. The original name "Klotho" (derived from Greek mythology) illustrates the high expectations regarding new insights, as decreasing Klotho levels in CKD could possibly explain the premature aging of multiple organ systems. In fact, the

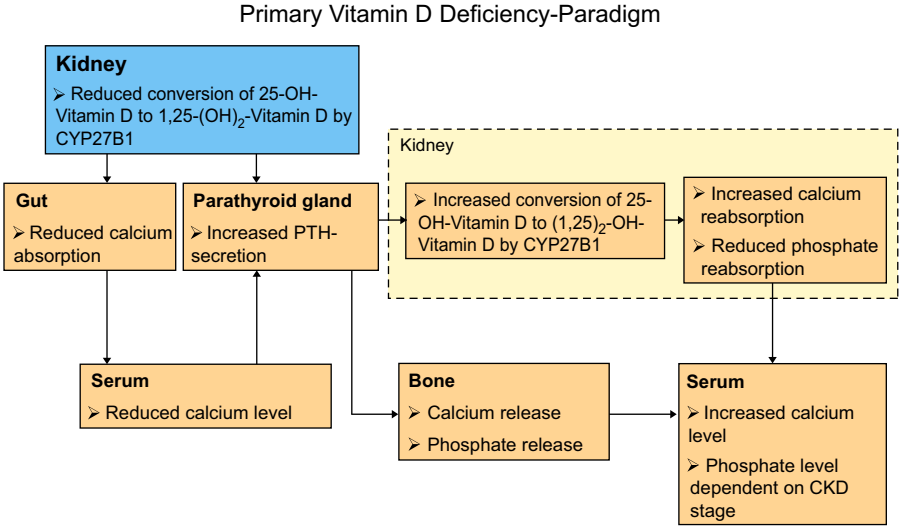

Figure 2. Primary phosphate-based regulative mechanisms. CKD, chronic kidney disease; PTH, parathyroid hormone. *Note*. From "Calcimimetics or vitamin D analogs for suppressing parathyroid hormone in end-stage renal disease: time for a paradigm shift?", by J.B. Wetmore and L.D. Quales, 2009, *Natl Clin Pract Nephrol 5*, p. 24. Copyright 2008, Nature Publishing Group. Adapted with permission.