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Review

Vitamin D and the kidney

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ABSTRACT

The kidney is essential for the maintenance of normal calcium and phosphorus homeostasis. Calcium and inorganic phosphorus are filtered at the glomerulus, and are reabsorbed from tubular segments by transporters and channels which are regulated by 1α,25-dihydroxyvitamin (1α,25$(OH)_2$D) and parathyroid hormone (PTH). The kidney is the major site of the synthesis of 1α,25$(OH)_2$D under physiologic conditions, and is one of the sites of 24,25-dihydroxyvitamin D (24,25$(OH)_2$D) synthesis. The activity of the 25(OH)D-1α-hydroxylase, the mixed function oxidase responsible for the synthesis of 1α,25$(OH)_2$D, is regulated by PTH, 1α,25$(OH)_2$D, fibroblast growth factor 23 (FGF23), inorganic phosphorus and other growth factors. Additionally, the vitamin D receptor which binds to, and mediates the activity of 1α,25$(OH)_2$D, is widely distributed in the kidney. Thus, the kidney, by regulating multiple transport and synthetic processes is indispensible in the maintenance of mineral homeostasis in physiological states.

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Introduction

The kidney has a unique function in mineral homeostasis. Both calcium and phosphorus are filtered, reabsorbed and excreted in the urine to a varying degree, generally in amounts that reflect the endogenous requirements of the two substances. The vitamin D-endocrine system plays a key role in controlling the renal excretion of both calcium and phosphorus. The reabsorption of calcium in the kidney is controlled by several factors, including 1α,25-dihydroxyvitamin D (1α,25$(OH)_2$D)[1] [1–5]. The kidney is the major site of synthesis of 1α,25$(OH)_2$D, the active, hormonal form of vitamin D [6–8]. The renal 25-hydroxyvitamin D_3 1α-hydroxylase (1α-hydroxylase) and 25-hydroxyvitamin D-24-hydroxylase (24-hydroxylase), and other 1α,25-dihydroxyvitamin D_3 and vitamin D analog metabolizing enzymes are expressed in kidney tissue [9–11]. The kidney expresses the vitamin D receptor (VDR) [11,12]. The kidney expresses several 1α,25$(OH)_2$D-dependent proteins that are important in calcium reabsorption e.g. the plasma membrane calcium pump (PMCa) [13–15], the epithelial calcium channel (ECaC) [16], the sodium calcium exchanger [17], and the calbindins [13–15]. Finally, the kidney has an important role in the control of plasma phosphate, which following filtration in the glomerulus is reabsorbed in nephron segments at a rate influenced by many of the same hormones and factors involved in calcium regulation [18–23].

To understand how vitamin D influences the efficiency of calcium and phosphorus reabsorption, a brief review of normal calcium and phosphorus handling by the kidney follows.

Calcium and phosphorus filtration and reabsorption in the kidney

Calcium handling by the kidney

On account of protein-binding, slightly more than half of total plasma calcium (plasma concentration 10 mg/dL or 2.5 mM) is filtered at the glomerulus [24]. The concentration of calcium in the glomerular filtrate is the same as that of plasma ultra-filterable calcium [25–27]. Assuming a glomerular filtration rate of 140 L per day and an ultrafiltrable calcium of 5.5 mg/dL, about 8000 mg of calcium are filtered by the kidney in 24 h; 98% of the filtered load of calcium is reabsorbed, resulting in an excreted calcium of about 150–200 mg/24 h [1,24]. Fifty to sixty percent of the filtered load of calcium is reabsorbed in the proximal tubule [2,3,28] by sodium-dependent, para-cellular mechanisms. Inhibition of sodium-potassium ATPase activity by ouabain reduces the amount of calcium reabsorbed in the proximal tubule, as does the substitution of sodium with lithium [29]. A reduction of tubular sodium

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[1] *Abbreviations used:* 1α,25$(OH)_2$D, 1α,25-dihydroxyvitamin D; ECaC, epithelial calcium channel; PMCa, plasma membrane calcium pump; VDR, vitamin D receptor.

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reabsorption by volume expansion inhibits proximal tubule calcium reabsorption, while an increase in sodium reabsorption associated with volume contraction, enhances proximal tubule calcium reabsorption [2,29]. Importantly, calcium reabsorption in the proximal tubule is not altered by thiazide diuretics, hormones such as PTH or 1α,25(OH)$_2$D$_3$, or by hydrogen ions [2,3,28,29]. Vitamin D-dependent proteins that play a role in trans-cellular calcium transport, such as the calbindins, ECaCs, and the PMCa pump are either not expressed in the proximal tubule, or are expressed in low amounts when compared with the amounts expressed in the distal tubule. Minimal amounts of calcium are absorbed in the descending loop and the thin ascending limb of the loop of Henle. About 20% of the filtered load of calcium is reabsorbed in the thick ascending limb of the loop of Henle; another 10–15% of filtered calcium is reabsorbed in the distal tubule with the remaining 5% being reabsorbed in the collecting duct [2,3,28,29]. The movement of calcium in the distal nephron is energy dependent and occurs against a concentration gradient; furthermore, the tubular lumen is electro-negative and becomes progressively more so towards the end of the distal tubule [30,31]. In the distal nephron, calcium reabsorption can be dissociated from sodium reabsorption by thiazide diuretics which inhibit sodium reabsorption but enhance calcium reabsorption [30,31]. In contrast to the proximal tubule, where hydrogen ion have no effect on calcium reabsorption, in the distal nephron hydrogen ions inhibit calcium reabsorption.

Phosphate handling by the kidney

Inorganic phosphate in the serum is freely filtered at the glomerulus [18–20]. About 80% of filtered phosphorus is reabsorbed in the proximal tubule [18]. The amount of phosphorus reabsorbed in the proximal tubule is greatest in the first half of the proximal tubule with some further phosphorus reabsorption occurring in the pars recta [18]. Little or no phosphorus reabsorption occurs in the loop of Henle or the distal tubule. The reabsorption of phosphate is sodium-dependent and is mediated by sodium-phosphate co-transporters (Na-Pi IIa, SLC34A1; Na-Pi IIc, SLC34A3, and Pit-2, SLC20A2) [32,33]. Na-Pi IIa activity is increased by a low phosphate diet and decreased by PTH [34–37]. The recently described phosphatonins, fibroblast growth factor-23 (FGF-23), MEPE and secreted frizzled related protein-4 (sFRP-4), inhibit sodium dependent phosphate transport [23,38]. In opossum kidney (OK) cells, NaPi II is internalized from the cell membrane in response to FGF-23 and sFRP-4, similar to the effects of PTH [39,40]. Additional factors involved in phosphorus reabsorption are noted in Table 1.

Table 1
Factors that alter renal phosphate excretion.

Increase	Decrease
1. High phosphate diet	1. Low-phosphate diet
2. Parathyroid hormone	2. Parathyroidectomy
3. Calcitonin	3. Thyroxine
4. Chronic vitamin D	4. Acute vitamin D
5. Glucagon	5. Insulin
6. Glucocorticoids	6. Growth hormone
7. Volume expansion	7. Volume contraction
8. Increased pCO_2	8. Decreased pCO_2
9. Chronic acidosis	
10. Starvation	
11. Diuretics	
12. "Phosphatonin"	
FGF-23	
sFRP-4	

Role of the kidney in the metabolism of 25OH D

The 25-hydroxyvitamin D$_3$-1α-hydroxylase and the synthesis of 1α,25(OH)$_2$D$_3$

25-Hydroxyvitamin D$_3$-1α-hydroxylase is a multi-component, cytochrome P-450 containing enzyme present in mitochondria of renal proximal tubular cells which transfers electrons from NADPH to the cytochrome P450, Cyp27B1 [7,41–53,6,54,55]. The latter, using molecular oxygen, converts 25-hydroxyvitamin D$_3$ (25(OH)D$_3$) to 1α,25(OH)$_2$D$_3$ and water. Nephrectomy greatly decreases circulating 1α,25(OH)$_2$D$_3$ concentration *in vivo* except during pregnancy, granuloma-forming diseases, and lymphomas associated with the ectopic production of 1α,25(OH)$_2$D$_3$ [54–59]. While the kidney is the major site of 1α,25(OH)$_2$D$_3$ production, 25(OH)D$_3$-1α-hydroxylase activity has been found *in vitro* in several other cell types [49,60–71]. *In vitro*, chick renal epithelial cells in culture, mammalian nephron segments and homogenates derived from avian and mammalian (mostly rodent) renal cells metabolize 25(OH)D$_3$ to 1α,25(OH)$_2$D$_3$ [72–76]. Proximal and distal tubular segments synthesize 1α,25(OH)$_2$D$_3$ [77,78]. Zehnder et al. have demonstrated the presence of 1α-hydroxylase mRNA and protein in the distal convoluted tubule, cortical collecting duct, thick ascending limb of the loop of Henle, and Bowman's capsule [78]. Recent experiments in which the 25(OH)D$_3$-1α-hydroxylase cytochrome P$_{450}$ gene (*Cyp27B1*) was deleted in mice, point to the central role of this enzyme in vitamin D metabolism [79]. Table 2 summarizes some of the key factors known to regulate the activity of this enzyme *in vivo* and *in vitro*. The major regulators appear to be PTH, inorganic phosphorus and 1α,25(OH)$_2$D$_3$ itself. Fibroblast growth factor 23 (FGF 23), and its binding protein Klotho that is produced mainly in the distal tubule, and which is essential in mediating FGF 23 activity, inhibit 25(OH)D$_3$-1α-hydroxylase activity and regulate the production of 1α,25(OH)$_2$D$_3$ [80–92]. Indeed, FGF 23 may mediate the effects of changing dietary phosphorus on 1α,25(OH)$_2$D$_3$ production. Regulators such as 1α,25(OH)$_2$D$_3$ which alter the expression of the *Cyp27B1* gene have reciprocal effects on the expression of the *Cyp24A1* gene [93] that are mediated via vitamin D-response elements in the promoters of the respective genes [94,95]. In cell culture, the extra-renal 25(OH)D$_3$-1α-hydroxylase is regulated by nitric oxide and by activation of toll-like receptors [65–71].

Table 2
Effect of increased level or activity of various factors on 1α,25(OH)$_2$D$_3$ concentration or 1α-hydroxylase activity.

Factor	Animals	Humans	Refs.
Parathyroid hormone	↑	↑	[27,74,290–298]
Serum inorganic phosphorus	↓	↓	[126,299–301]
1α,25(OH)$_2$D$_3$	↓	↓	[290,302]
Calcium (direct)	?	↓	[303,304]
Calcitonin	↑,↓,0	↑	[24,74,290,291,305,306]
Hydrogen ion	↓	0	[292,307,308]
Sex steroids	↑	↑	[125,309]
Prolactin	↑	0	[310–312]
Growth hormone and insulin-like growth factor-1	↑	↑,↓,0	[224,304,313–318]
Glucocorticoids	↓,0	↑,↓,0	[182,319–322]
Thyroid hormone	?	↓[a]	[323–325]
Fibroblast growth factor 23/ Klotho axis	↓	?	[80–92]
Frizzled related protein 4	↓	?	[23]
Pregnancy	↑	↑[a]	[326,327]

↑, Stimulation or increase; ↓, suppression or decrease; 0, no effect; ?, effect not known.

[a] Effects may be secondary to changes in calcium, phosphorus or parathyroid hormone (with permission, modified from Kumar [93]).