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Review Article

Possible Metabolic Alteration and Endocrinological Dysregulation in Canine Chronic Kidney Disease with Renal Osteodystrophy: A Comprehensive Review

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Abstract

Chronic kidney disease (CKD) in dogs is associated with metabolic alterations and endocrinological dysregulation that can lead to renal osteodystrophy syndrome. This review article examines the complex abnormal signaling and interactions between circulating minerals, vitamins, hormones, cytokines, and fibroblast growth factor during CKD. Despite recent advances, the pathogenesis of renal osteodystrophy in CKD dogs remains unclear. This article includes recently published research and insights from authors to enhance our understanding of the basic mechanisms of kidney regulation and dysregulation in CKD dogs.

Keywords: CKD; Signalling; Calcium; Osteodystrophy; PTH

Introduction

Renal osteodystrophy fibrosa is a common sequela of canine chronic kidney disease, also known as renal osteitis fibrosa, rubber jaw syndrome, renal rickets, or fibrous osteodystrophy [1]. It is defined by KDIGO 2005 as an alteration of bone morphology in patients with CKD. The overall frequency was reported to be 76% in dogs with chronic kidney disease (CKD) and it might be 100% in dogs with end stage CKD [3]. In CKD, there is a disruption in the balance of minerals such as calcium and phosphorus, leading to decreased levels of calcium and increased levels of phosphorus in the blood. Over time, this can lead to bone resorption, weakening of the bones, and the development of renal osteodystrophy [2]. It results of a complex abnormal signalling and interactions between circulating ionized calcium (iCa), inorganic phosphorus (Pi), parathyroid hormone (PTH), calcidiol (25(OH)-vitamin D),calcitriol (1,25(OH)2-vitamin D), cytokines and fibroblast growth factor 23 (FGF-23) occur during CKD, but pathogenesis until not clear [5,13]. To understand the possible mechanisms following chronic kidney disease (CKD) leading to renal osteodystrophy, it's important to consider the interplay of various factors.

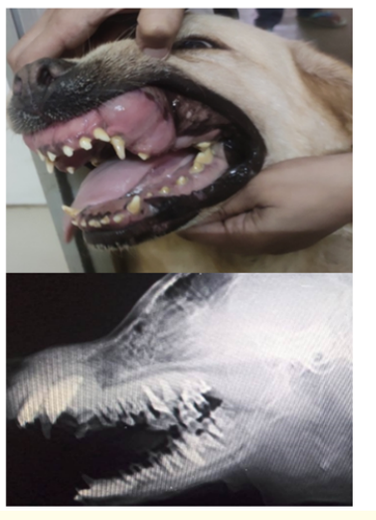

Figure 1: Clinical and radiograph views of jaw bone with Renal associated osteodystrophy

Metabolic alterations in chronic renal disease

Physiologically, the kidney plays a master role in regulating calcium, phosphorus, and vitamin D levels in circulation. The regulation of serum calcium concentration is a complex process that requires the actions of parathyroid hormone (PTH), vitamin D, calcitonin, and ionized calcium (iCa) for sensing calcium receptors [10]. PTH is largely responsible for the minute-to-minute control of serum iCa concentration, whereas calcitriol maintains day-to-day control of serum iCa concentration. The intestine, kidney, and bone are the major target organs affected by calcium regulatory mechanism. Phosphate comprises about 1% of total body weight; about 85% resides in bone, 14% in cells, and 1% in serum and ECFs. Classically, there are 4 main known regulators of phosphate metabolism: (a) dietary phosphate intake and absorption, (b) calcitriol, which can increase phosphorus resorption from bone and absorption from intestine, (c) PTH, which directly causes phosphorus resorption from bone, and indirectly activates intestinal absorption through stimulation of calcitriol production, and (d) renal tubular reabsorption of phosphorus that is stimulated by tubular filtered load of phosphorus and inhibited by PTH. Both of these minerals are present in bone as hydroxyapatite Ca10 (PO4)6$(OH)_2$ and it necessary for structural hardness and strength (15). In healthy dogs, the serum level of ionized calcium (iCa) 9–10 mg/dL and phosphorus (iP) are 2.0 and 3.0 mmo1/1 and they are key regulators to maintain the calcium and phosphorus haemostatic balance between bone, extracellular and intestinal absorption. Physiologically, calcium and phosphate is freely filtered through the glomerulus and reabsorbed via the renal sodium/phosphate type 2, co -transporters NaPi-IIa and NaPi-IIc, which are expressed on the luminal side of the proximal tubular epithelial cells [11].

In chronic disease, excessive damaged of renal proximal tubular epithelial cells (PTECs) lead to two main alteration reduced the conversion of active form of vitamin D and dysregulatrion of phosphate [1]. Most of the researcher hypothesized that reduced the conversion of active form of vitamin D is the prime point of genesis of abnormal renal secondary hyperparathyroidism. However, dysregulatrion of phosphate in body play pivotal role in possible endocrinopathy. Untreated renal secondary hyperparathyroidism leads to altered bone histology, bone fragility, skeletal deformities, growth retardation, and cardiovascular calcifications. Due to reduction in GFR and functional loss of PCT, decreases the apical expression of NaPi-IIa and NaPi-IIc in the proximal tubules of the kidney retarded renal Pi excretion resulted retention of inorganic phosphorus in serum leads to hyperphosphatemia [5,8]. Increased plasma phosphorus concentration causes a reciprocal decrease in ionized calcium concentration via the law of mass action lead to abnormal hypocalcaemia. At the same time another possible mechanism can also contributes to established a hypocalcaemia condition that is, insufficient conversion of vitamin D into active form of vitamin D due to lack of enzyme 1 alpha hydrolyse of PCT [9]. Deficiency of calcitriol directly act on enterocytes to decreased intestinal absorption of calcium and phosphorus. Hyperphosphatemia and hypocalcaemia further instigates abnormal signalling to parathyroid gland to releases excess parathyroid hormone [7,9].

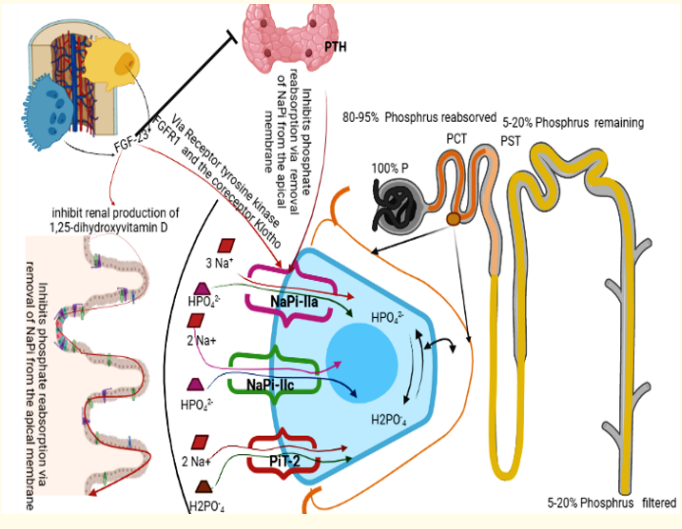

Figure 2: Regulation of Phosphate ions in cellular component of PCT

Possible endocrinopathy dysregulation in chronic renal disease

The possible endocrinopathy have been postulated that parathyroid hormone (PTH), calcidiol (25(OH)-vitamin D), calcitriol (1,25(OH)2-vitamin D), and fibroblast growth factor 23 (FGF-23) are the key player that might be involved in the dysregulatrion of calcium and phosphate in CKD [4]. After damaged PCT, hyperphosphatemia continues functionally instigates the parathyroid gland that lead to parathyroid cell proliferation and hyperplasia [6]. Excessive secretions of PTH further reduced the secretion of calcitriol hormone and increase the amount of FGF 23 from bone cells. As a primary regulator of mineral ion homeostasis, PTH directly targets the proximal convoluted tubules (PCT) of the remaining kidney where it mediates the down-regulation of sodium-dependent phosphate co-transporters, NPTIIa, NPTIIc and PiTII, and enhances the expression of 25-hydroxyvitamin D3 1α-hydroxylase, leading to an increase in the bioactive form of vitamin D. An increased PTH level can have deleterious effects, including soft tissue mineralization, fibrous osteodystrophy, bone marrow suppression.

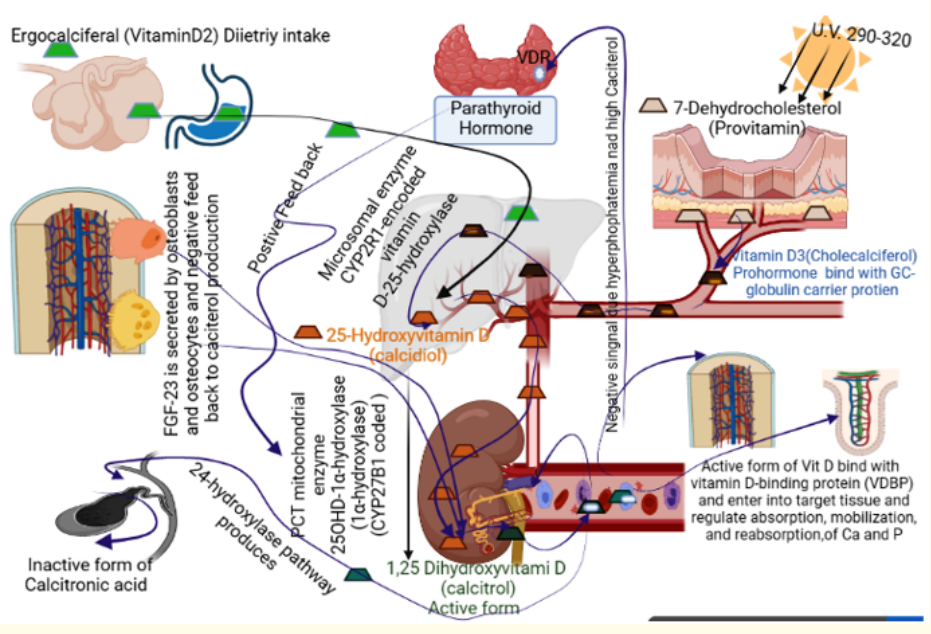

Figure 3: Regulation of PTH-,Calictrol and FGF-23 axis.

FGF-23 a potent phosphaturic glycoprotein secreted by osteoblasts and osteocytes, which binds to the fibroblastic growth receptor 1 (FGFR1) in the presence of its coreceptor Klotho. It has emerged as a central factor in calcium and phosphate homeostasis and vitamin D metabolism in mammals. Progressive CKD also leads to an increase in FGF-23, which leads to enhanced activity of 24-hydroxylase, thereby increasing the degradation of calcidiol to 24,25(OH)2-vitamin D. Resulted increase the serum calcium level by increasing calcium reabsorption from the renal proximal tubules and intestinal absorption. It also acts on bone tissue to increase calcium reabsorption from the bone matrix to elevate the serum calcium level, principally by stimulating osteoclasts, which digest bone matrix and increase the calcium ion level in the matrix fluid. Calcium ions are then transported from the bone fluid to the extracellular fluid via an extensive membrane system formed by the processes of osteocytes and osteoblasts. Its levels increase progressively beginning in early CKD, presumably as a physiological adaptation to maintain normal serum phosphate levels or normal phosphorus balance. FGF23 is emerging as a novel and early biomarker that may help identify which CKD dog might benefit most from aggressive management of disordered phosphorus metabolism. Over all endocrinopathological contributes to demineralization of maxiolo-facial bone particularly mandible resulted pathological fracture of jaw and loosening of teeth [16].

Conclusions

In chronic kidney disease (CKD), the excessive damage to nephrons leads to irreversible and progressive loss of the filtration capacity of glomeruli, absorption capacity of proximal tubules, and synthesis of 1 alpha hydroxylase enzyme. The retention of phosphorus and abnormally lower serum calcium levels trigger excess parathyroid hormone (PTH) secretion, leading to parathyroid cell proliferation and hyperplasia .Recently, other hypotheses have been postulated, suggesting that fibroblast growth factor-23 (FGF-23) also plays a role in bone deformities and emerges as a novel and early biomarker that may help identify which CKD patients are at risk .In addition, some cytokines are also being investigated for their potential involvement in bone remodeling, especially transforming growth factor-beta (TGF-beta), which is synthesized by osteoblasts and osteoclasts under the control of PTH and stored in the bone matrix.

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