Studies on the clinical significance of serum fibroblast growth factor-23 concentration in dogs and cats with chronic kidney disease

Summary of Doctoral Thesis

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Fibroblast growth factor (FGF)-23 is a phosphaturic hormone secreted by osteocytes in response to increased blood phosphate and calcitriol levels. In humans, FGF-23 is involved in mineral metabolic disorders in chronic kidney disease (CKD), and its blood levels compensatively increase with phosphate accumulation in the body due to declining glomerular filtrate rate (GFR). In human CKD, increased blood FGF-23 concentrations occur earlier than the development of renal secondary hyperparathyroidism and hyperphosphatemia and are associated with a shorter survival time and CKD progression. Therefore, FGF-23 is considered an early marker of mineral metabolic disorders in CKD. Studies on FGF-23 have recently been reported in veterinary medicine. Although two studies have reported increased plasma FGF-23 concentrations in dogs with CKD, the sample sizes were small; therefore, further, larger investigations of FGF-23 in dogs with CKD are needed. In addition, the clinical importance of increased blood FGF-23 levels in dogs with CKD is unknown. In cats, plasma FGF-23 concentrations have been seen to increase with CKD stage and were associated with survival time and CKD progression. However, the studies targeted geriatric cats, and the relationship between CKD and FGF-23 in younger cats with CKD has not been investigated. Furthermore, although the association between FGF-23 and phosphate in cats has been investigated in various studies, few studies have reported the association between FGF-23 and blood calcium concentration in cats.

Thus, the present study investigated whether FGF-23 is an early marker of mineral metabolic disorders in canine CKD and whether its increased blood levels has clinical significance. In addition, our study evaluated the associations of FGF-23 with CKD stage in cats aged 1–8 years old and with blood calcium levels in cats with CKD and upper urolithiasis.

Evaluation of the clinical significance of serum FGF-23 concentration as an early marker of mineral metabolic disorder in canine CKD (Chapter 2)

This chapter examined the association of serum FGF-23 concentrations with CKD stage and other phosphate markers, such as intact parathyroid hormone (PTH) and phosphorus, in dogs. This chapter retrospectively evaluated the serum samples and medical records of 15 clinically healthy dogs (control group) and 75 dogs with CKD. Serum FGF-23 concentrations and other phosphate markers were compared between the control group and CKD stages according to the International Renal Interest Society (IRIS) guidelines. The upper limit of the reference range for serum FGF-23 concentration was derived from the control group, and the percentage of dogs with increased serum FGF-23 concentration in each CKD stage was evaluated. In addition, multiple regression analysis was performed to determine the predictors of FGF-23.

Serum FGF-23 concentrations was significantly higher in stage 2 dogs than in controls. Whereas 30.8% dogs with stage 2 developed hyperparathyroidism (intact PTH > 8.5 pg/mL), 73.1% dogs with stage 2 had elevated FGF-23 levels above the reference range (>528 pg/mL). Serum phosphorus concentrations were significantly higher only in stage 4. In multiple regression analysis, log creatinine, log intact PTH, and log product of total calcium and phosphorus were independent predictors of log FGF-23.

Serum FGF-23 concentrations in dogs with CKD increased earlier than serum intact PTH and phosphorus concentrations. Therefore, FGF-23 was determined to be an early marker of mineral metabolic disorders in canine CKD.

Evaluation of the clinical significance of increased serum FGF-23 concentration in dogs

with CKD without hyperphosphatemia (Chapter 3)

This chapter investigated whether serum FGF-23 concentration in normophosphatemic dogs with CKD is associated with the risk of subsequent hyperphosphatemia and CKD progression. This study retrospectively investigated the serum samples and medical records of 42 dogs with CKD without hyperphosphatemia. Hyperphosphatemia was defined as a serum phosphorous concentration > 5.0 mg/dL. Progression was defined as a >1.5-fold increase in serum creatinine concentration. The time periods for these outcomes between groups were compared using the Kaplan–Meier curve and log-rank test. The hazard ratios for the outcomes were assessed using univariate and multivariate Cox regression analyses.

Serum FGF-23 concentration > 528 pg/mL was associated with a shorter time to the development of hyperphosphatemia and CKD progression. In multiple Cox regression analysis, increased FGF-23 concentration remained a significant variable associated with these outcomes.

Increased serum FGF-23 concentration in normophosphatemic dogs with CKD was associated with the significant risk of developing hyperphosphatemia and CKD progression. Thus, serum FGF-23 concentration should be reduced to at least delay these conditions in normophosphatemic dogs with CKD.

Comparison between serum FGF-23 concentration and CKD stage in young and adult cats (Chapter 4)

This chapter evaluated serum FGF-23 concentrations in young and adult cats with CKD. The chapter retrospectively investigated the serum samples and medical records of clinically healthy cats aged 1–8 years (control group, n = 7) and cats with CKD

(n = 54). Cats with CKD were divided into four stages according to the IRIS CKD guidelines. Serum FGF-23 concentrations were compared between cats in the control group and CKD groups. Continuous variables were analyzed using correlations and multiple linear regression.

Serum FGF-23 concentrations were significantly higher in cats with stages 1–4 CKD compared with the control group. Additionally, serum FGF-23 concentration in cats with stage 3–4 CKD was higher than in those with IRIS stages 1 and 2 CKD. On the other hand, no significant difference in serum phosphorus concentration was found between groups. Multiple linear regression analysis identified serum log urea nitrogen concentration, log serum phosphorus concentration, and log blood ionized calcium concentration as independent variables predicting log serum FGF-23 concentration.

Serum FGF-23 concentrations in young and adult cats with CKD increased with CKD stage and were associated with serum phosphorus and blood ionized calcium concentrations. In addition, although serum phosphorus concentration did not differ significantly between groups, serum FGF-23 concentrations significantly increased in CKD stage 1 compared with that in the control group. These results are consistent with those of the previous studies on geriatric cats, further affirming FGF-23 as an early marker of mineral metabolic disorders in CKD in younger cats.

Evaluation of association between serum FGF-23 concentrations and blood calcium levels in CKD cats with upper urolithiasis (Chapter 5)

This chapter examined whether serum FGF-23 concentration is associated with serum total calcium and blood ionized calcium concentrations in cats with CKD and upper urolithiasis. Serum samples and medical records of 32 cats with CKD with nephrolith,

ureterolith, or both were investigated retrospectively. Cats with serum creatinine concentrations > 2.8 mg/dL and/or serum phosphorus concentration ≥ 4.5 mg/dL were excluded to minimize the effect of GFR and phosphorus status on serum FGF-23 concentration. Based on the cut-off value for serum total calcium (11.5 mg/dL) or blood ionized calcium (1.40 mmol/L), cats were divided into the following groups: H-tCa (>11.5 mg/dL) and N-tCa (≤11.5 mg/dL) groups or H-iCa (>1.40 mmol/L) and N-iCa (≤1.40 mmol/L) groups, respectively. Serum FGF-23 concentrations were compared between groups, and correlation analysis for serum FGF-23 concentrations was performed.

Serum FGF-23 concentrations in the H-tCa and H-iCa groups were significantly higher than those in the N-tCa and N-iCa groups, respectively. Serum FGF-23 concentrations were significantly correlated with serum total calcium and blood ionized calcium concentrations, but not serum creatinine or phosphorus concentrations.

Increased serum FGF-23 concentration was associated with hypercalcemia independently of GFR and phosphate status in cats with CKD and upper urolithiasis. As demonstrated in previous studies on rodent, the results in this chapter suggest that hypercalcemia can induce increased serum FGF-23 concentration in cats.

In conclusion, the present study determined that increased serum FGF-23 concentrations in dogs with CKD occurred earlier than the development of renal secondary hyperparathyroidism and hyperphosphatemia. In addition, increased serum FGF-23 concentrations in dogs with CKD without hyperphosphatemia indicate a risk of developing hyperphosphatemia and CKD progression. FGF-23 can thus be used to indicate intervention by phosphate-restricted therapy in dogs. In cats, FGF-23 was also

determined as an early marker of mineral metabolic disorders in CKD, confirming the results of a previous study on geriatric cats. Additionally, the present study determined that hypercalcemia in cats with CKD and upper urolithiasis was associated with increased FGF-23 concentration.