J Vet Clin 25(4) : 236-240 (2008)

Journal of Veterinary Clinics
www.ksvc.or.kr

Relationship between Calcium/Inorganic Phosphorus and Parathyroid Hormone Concentrations in Dogs with Renal Failure

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(Accepted : July 31, 2008)

Abstract : Parathyroid hormone (PTH) regulates calcium (Ca) and phosphate transport. Secondary hyperparathyroidism usually occur in chronic renal failure (CRF), and it is a common complication of CRF in dogs and cats. Twenty one dogs with renal failure were enrolled in this study. Plasma Ca, inorganic phosphorus (iP) and PTH concentrations were measured. Dogs were divided into two groups by the ratio of Ca to iP (Ca/iP$\leq$1; Group I, Ca/iP$\geq$1.5; Group II). The PTH level between sexes ages were not significantly different. The PTH level and Ca/iP between two groups were significantly different ($p < 0.0001$). In conclusion, The ratio of Ca to iP may be considered as useful surrogator to predict PTH level of dogs with renal failure.

Key words **:** Ca, inorganic phosphorus, parathyroid hormone, renal failure, dogs.

Introduction

Parathyroid hormone (PTH) regulates calcium (Ca) and phosphate transport. It maintains normal serum Ca levels by enhancing Ca uptake from the bones, kidneys and intestines, and increasing inorganic phosphorus (iP) excretion by the kidney (5,8).

Hyperparathyroidism was classified into two types. Primary hyperparathyroidism results from excessive secretion of PTH by one or more abnormal parathyroid glands. This disease has been reported sporadically in dogs and cats and is characterized by persistent and long-standing hypercalcemia (6). Secondary hyperparathyroidism results from other causes, such as nutrition, renal dysfunction and so on. Serum Ca and iP concentration and abnormal mechanism of these are closely related with renal hyperparathyroidism. Secondary hyperparathyroidism occur in all animals with renal failure, especially chronic renal failure (CRF), and it is a common complication of CRF in dogs and cats (5,9).

The metabolism of Ca and phosphorus is considerably disturbed in uremia, and it is involved in the development of renal hyperparathyroidism, although hypocalcaemia and hyperphosphataemia are not definitive in the early stages of renal failure (19). The development of hyperphosphataemia in the final stages of CRF is well known, having been widely described both in clinical cases and in experimental models (7,16,21,22).

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In this study, relationship between renal secondary hyperparathyroidism and patient's factors (sex and age), and relationship between PTH level and Ca/iP (ratio of Ca to iP) was investigated.

Materials and Methods

Animals

Twenty one dogs were enrolled in this study. They were diagnosed as renal failure in local animal clinics and the Veterinary Medical Teaching Hospital, College of Veterinary Medicine. Konkuk University between September 2003 and August 2004.

Ten dogs had an imbalance ratio of blood calcium and inorganic phosphorus (Ca/iP $\leq$ 1; Group I). Another 11 dogs had normal ratio of blood calcium and inorganic phosphorus (Ca/iP $\geq$ 1.5; Group II). Age, sex and breed of dogs with renal failure were shown in Table 1.

Renal failure was classified into acute and chronic according to history and response to treatment.

Measurement of Ca, iP and PTH concentration in blood

Blood samples were obtained by cephalic venipuncture upon presentation. Samples were collected in heparinized tubes, and plasma was harvested after centrifugation.

The level of Ca, iP and albumin was measured using automatic dry chemistry analyzer (FUJI DRI-CHEM 3500i; Fuji photofilm Co., Ltd., Tokyo, Japan). Changes in serum concentration of albumin and globulins may alter the measured total serum calcium concentration without altering ionized

calcium levels (5), thus corrected total Ca was calculated as follows (13). Corrected total Ca (mg/dL) = measured total Ca (mg/dL)-albumin (mg/dL) + 3.5.

The plasma PTH level was measured by a commercially available immunoradiometric assay (Coat-A-Count Intact PTH IRMA; Diagnostic Products Corporation, LosAngeles, USA).

Data analysis

The age of enrolled dogs was classified into 3 groups as follows: one to 48 months (A1), 49 to 96 months (A2) and 96 to 147 months (A3). The PTH level between male and female, and between Group I and Group II, and Ca / iP (ratio of Ca to iP) between Group I and Group II were compared using Mann-Whitney U-test. The PTH level between A1, A2 and A3 was compared using the Kruskal-Wallis test.

A value of $p < 0.05$ was considered significant. The statistical analyses were performed with SPSS (version 12.0; SPSS Inc, Chicago, USA).

Results

Age, breed and sex of enrolled dogs

The mean age of clinically secondary hyperparathyroidism dogs was 75 months (6 to 147 months). Female in all case, Group I and Group II was 52.4% (11/21), 50% (5/10) and 54.5% (6/11), respectively. Breeds were Poodle (9.5%; 2/21), Maltese (9.5%; 2/21), Yorkshire terrier (4.7%; 1/21), Shih-

Table 1. Breed, age, sex and final diagnosis of enrolled dogs

Group	No	Breed	Age[1]	Sex	Final diagnosis
I	1	Cocker spaniel	6	F	CRF
	2	Cocker spaniel	20	F	CRF
	3	Mixed breed	48	M	CRF
	4	Mixed breed	84	M	CRF
	5	Poodle	147	M	CRF
	6	Golden Retriever	12	M	CRF
	7	Schnauzer	24	M	CRF
	8	Schnauzer	48	F	ARF
	9	Schnauzer	60	F	CRF
	10	Shih-Tzu	16	F	CRF
II	1	Chihuahua	48	F	CRF
	2	Maltese	36	F	CRF
	3	Maltese	72	M	CRF
	4	Mixed breed	108	M	CRF
	5	Poodle	24	F	ARF
	6	Schnauzer	48	F	CRF
	7	Shih-Tzu	30	M	CRF
	8	Shih-Tzu	48	F	CRF
	9	Shih-Tzu	72	M	CRF
	10	Shih-Tzu	96	F	ARF
	11	Yorkshire terrier	132	M	CRF

F: Female, M: Male, ARF: Acute renal failure, CRF: Chronic renal failure.
[1]Values were given as months.

Table 2. The parathyroid hormone level (mean ± SD) of renal failure dogs between sexes age groups

Factor	Classification	Total	Group I	Group II
Sex	M	875.27 ± 687.50	1435.44 ± 238.60	175.05 ± 88.14
	F	621.88 ± 605.59	1287.76 ± 230.81	146.24 ± 58.30
Age	A1	865.09 ± 667.27	1381.21 ± 259.32	142.52 ± 68.90
	A2	506.33 ± 547.17	1208.95 ± 119.71	155.03 ± 23.37
	A3	640.27 ± 777.02	1529.60[a]	195.6 ± 145.38

F: Female, M: Male, A1: One to 48 months, A2: 49 to 96 months, A3: 96 to 147 months.
[a]: enrolled subject was one dog.

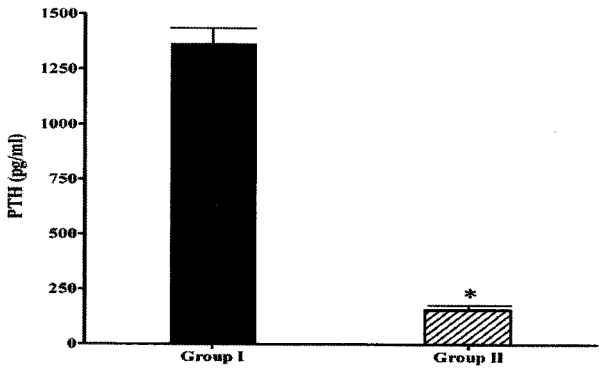

Fig 1. A comparison of plasma parathyroid hormone (PTH) level between imbalance (Group I) and normal (Group II) ratio of plasma calcium (Ca) and inorganic phosphorus (iP). Group I: Ca/iP≤1. Group II: Ca/iP≥1.5.
*: Significance different between Group I and Group II ($p < 0.05$).

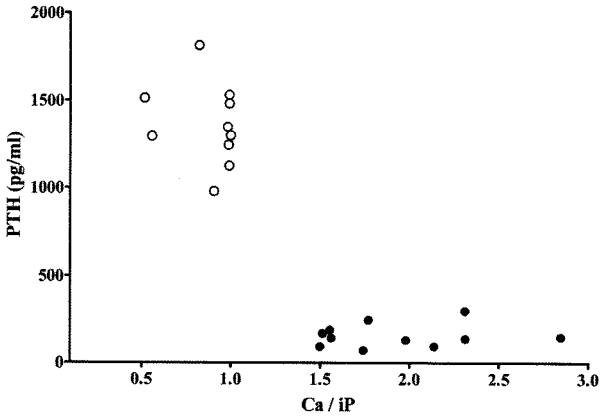

Fig 2. Relationship between plasma parathyroid hormone (PTH) level and ratio of plasma calcium (Ca) to inorganic phosphorus (iP). Open circles: Imbalance ratio of plasma Ca to iP group (Ca/iP≤1, Group I). Closed circles: Normal ratio of plasma Ca to iP group (Ca/iP≥1.5, Group II).

Tzu (23.8%; 5/21), Cocker spaniel (9.5%; 2/21), Chihuahua (4.7%; 1/21), Schnauzer (19%; 4/21), Retriever dog (4.7%; 1/21) and mixed dogs (14.3%; 3/21).

PTH level between sexes age

The comparison of the PTH level between sexes age was shown as Table 2. The PTH level between male and female was not significantly different ($p = 0.356$ in overall comparison, $p = 0.465$ in Group I and $p = 0.705$ in Group II). The PTH level between age groups was also not significantly different ($p = 0.675$ in overall comparison, $p = 0.255$ in Group I and $p = 0.763$ in Group II).

PTH level and Ca/iP (ratio of Ca to iP) between Group I and Group II

The PTH level of imbalance ratio group (Group I) and normal ratio group (Group II) of blood Ca and iP was 1361.60 ± 234.60 pg/ml and 156.72 ± 67.68 pg/ml, respectively (Fig 1). The PTH level between two groups was significantly different ($p < 0.0001$).

Relationship between PTH level and Ca/iP was shown as Fig 2. Mean value of Ca/iP of Group I and Group II were 0.88 ± 0.19 and 1.93 ± 0.43, respectively, and Ca/iP between two groups was significantly different ($p < 0.0001$).

Discussion

While primary parathyroid gland disease is rare in dogs, secondary hyperparathyroidism can occur frequently in patients with renal failure or malnutrition. Hyperparathyroidism occurred in 100 per cent of cats with end-stage of CRF and 47 per cent of clinically normal cats with only biochemical evidence of CRF (3). The pathogenesis of hyperparathyroidism in CRF is obscure. In early to moderate renal failure, the increasing of PTH level prevents hypocalcemia, hyperphospatemia, and the decrease of calcitriol. However, in end-stage of CRF, hyperphosphatemia, low circulating calcitriol level and reduced blood ionized calcium concentration occurs. The elevated concentrations of PTH may be sufficient to stimulate calcitriol synthesis to normal levels in early CRF. However, as renal disease advances, structural damages of the kidney limit the renal capacity to both excrete phosphate and synthesis calcitriol (2,9,14).

This secondary hyperparathyroidism can be improved by correcting of primary causes, and relationship between serum PTH level and serum Ca/iP should be considered. Whether the values of Ca/iP are calculated as normal or imbalance should be first considered as well as history of renal failure and nutritional condition before PTH concentration is evaluated (5,8). Calcium level has been considered as the main factor responsible for the genesis of secondary hyperparathyroidism in chronic renal disease (3,12). However, Ca level may not be essential for the development of secondary hyperparathyroidism in CRF (4,18). Recently, it is accepted that PTH may be increased by only phosphate retention via indirect mechanisms, which affect Ca regulation and calcitriol synthesis (17,20). However, a recent in vitro study have suggested that phosphate may directly affect PTH secretion (23). According to a previous study (1), phosphate level in early CRF should be controlled to prevent and treat secondary hyperparathyroidism.

The ratio of blood Ca to iP may be considered as potential factor for secondary hyperparathyroidism owing to renal failure (11,15). It was also used for monitoring bone mineralization and cardiac disease (2,10). In this study, twenty one dogs had history of renal failure. Almost dogs were diagnosed as CRF, and had various PTH level (from 71.2 to 1813.3 pg/ml). Main factor of dividing group in this study was ratio of Ca to iP (Ca/iP ≤1; Group I, Ca/iP ≥1.5; Group II). The PTH level and Ca/iP (ratio of Ca to iP) between two groups was significantly different ($p < 0.0001$). Thus, ratio of Ca to iP

(Ca/iP) may be considered as an useful surrogator to predict PTH level of dogs with renal failure.

Acknowledgement

This work was Supported by the Konkuk University.

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신부전증의 개에서 혈중 칼슘/무기인과 부갑상샘 호르몬의 관계

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요 약 : 부갑상샘 호르몬 (PTH)은 칼슘과 무기인의 수송을 조절한다. 속발성 부갑상샘 기능항진증은 대개 만성신부전에서 발생하고, 이는 개와 고양이에 있어서 CRF의 일반적인 합병증이다. 신부전을 갖는 21마리의 개가 본 연구에 사용되었다. 공시동물로부터 채혈한 혈액 중 칼슘 (Ca), 무기인 (iP), PTH의 농도를 측정하여 칼슘과 무기인의 비율에 따라 두 군으로 분류하였다 (Ca / iP ≤ 1; 그룹 I, Ca/iP ≥ 1.5; 그룹 II). 성과 연령 사이에 부갑상샘 호르몬 수준은 유의성 있는 차이가 없었다. 두 군 사이에 부갑상샘 호르몬 수준과 Ca/P의 비율에는 유의성 ($p < 0.0001$)있는 차이가 나타났다. 결론적으로, 칼슘과 무기인의 비율은 신부전을 갖는 개에서 부갑상샘 호르몬 수준을 예측하기 위한 지표로 이용될 수 있을 것으로 생각된다.

주요어 : 칼슘, 무기질 인, 부갑상샘 호르몬, 신부전, 개