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## Köpeklerde Böbrek Yetmezliği Şiddetinin Belirteçleri Olarak Gastrin, Amilaz, Homosistein ve Cystatin C'nin Değerlendirilmesi

Evaluation of Gastrin, Amylase, Homocysteine, and Cystatin-C as Indicators of Renal Failure Severity in Dogs

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### ÖZ

**Amaç:** Gastrin, amilaz, homosistein (Hcy) ve cystatin C (Cys-C) gibi belirteçlerin akut (ARF) ve kronik böbrek yetmezliğini (CRF) ayırt etmedeki potansiyel tanısal değeri, veteriner hekimlikte büyük ölçüde belirsizliğini korumaktadır. Bu çalışma, renal yetmezlikli köpeklerde bu dört biyobelirtecin tanısal potansiyelinin değerlendirilmesini amaçlamıştır. **Gereç ve Yöntem:** Toplam 45 köpek ARF'li, CRF'li ve sağlıklı kontroller olmak üzere üç gruba eşit şekilde ayrılmıştır. **Bulgular:** Serum kan üre nitrojeni (BUN), kreatinin ve Cys-C düzeylerinin, kontrol köpeklere kıyasla renal yetmezlikli köpeklerde arttığı saptanmıştır ( $p<0.001$ ). Ortalama serum gastrin, Hcy ve amilaz konsantrasyonları ARF'li köpekler ile kontroller arasında anlamlı fark göstermemiş, ancak CRF'li köpeklerde her iki gruba göre belirgin şekilde daha yüksek bulunmuştur ( $p<0.01-0.001$ ). **Sonuç:** Elde edilen bulgular, serum gastrin, amilaz ve Hcy'nin özellikle CRF'de artış eğiliminde olduğunu, ancak ARF ile CRF'yi tutarlı biçimde ayırt edebilen tek parametrenin serum cystatin C olduğunu göstermektedir. Bu kapsamlı değerlendirme, köpeklerde daha az kullanılan renal biyobelirteçlerin tanısal önemine ilişkin yeni bilgiler sunmakta ve cystatin C'nin böbrek hasarının kronikliğini ayırt etmede değerli bir belirteç olduğunu desteklemektedir.

### ABSTRACT

**Objective:** The potential diagnostic value of gastrin, amylase, homocysteine (Hcy), and cystatin C (Cys-C) in differentiating acute (ARF) from chronic renal failure (CRF) remains largely unclear in veterinary medicine. This study aimed to assess the diagnostic potential of these four biomarkers in dogs with renal failure. **Material and Methods:** A total of 45 dogs were divided equally into three groups: dogs with ARF, dogs with CRF, and healthy controls. **Results:** Serum blood urea nitrogen (BUN), creatinine, and Cys-C levels were found to have elevated in dogs with renal failure compared to controls ( $p<0.001$ ). Mean serum gastrin, Hcy, and amylase concentrations did not differ significantly between ARF dogs and controls, but were markedly higher in dogs with CRF than in the other two groups ( $p<0.01-0.001$ ). The findings indicate that although serum gastrin, amylase, and Hcy tend to increase primarily in CRF, serum cystatin C is the only parameter that consistently differentiates between ARF and CRF. **Conclusion:** This comprehensive analysis provides new insights into the diagnostic utility of less commonly used renal biomarkers in dogs and supports cystatin C as a valuable marker for distinguishing the chronicity of renal injury.

### INTRODUCTION

Renal failure is one of the most important health problems leading to a decrease in life expectancy and the quality of life in human and veterinary medicine.<sup>1</sup> Thus, early diagnosis of renal failure is of great importance to start medication immediately and modification for daily routines immediately, thereby slowing the disease progression.<sup>1,2</sup> For this reason, new and realistic biomarkers indicating the presence of renal injury before clinical signs are needed.

There are limited studies on whether serum gastrin, amylase, homocysteine (Hcy), and cystatin levels can be used as a renal injury marker, and no studies have investigated whether all or one of them may serve as a discriminator factor from acute (ARF) to chronic renal failure (CRF) in dogs. In general, studies about this subject have focused on the serum level of one of the biomarkers in patients (humans, cats, or dogs) with chronic kidney disease (CKD). Among them, elevated serum gastrin and Hcy levels were reported in dogs<sup>3</sup> and cats with CKD<sup>4</sup>, respectively.

On the basis of the existing experimental and clinical studies about the factors affecting the appearance of hypergastrinemia in renal failure, it can be concluded that the kidney plays an important role in the degradation of endogenous gastrin.<sup>5,6</sup> Individuals with impaired renal function have elevated serum gastrin levels, and gastrin circulates at higher than normal levels in patients with renal failure.<sup>5-9</sup> Serum gastrin rose proportionately with the degree of renal failure, making it a potential bio-indicator to estimate the glomerular filtration rate (GFR). There was a significant positive correlation between basal serum gastrin concentrations and the severity of renal damage in humans.<sup>6</sup>

Twenty percent of pancreatic enzymes is excreted by the kidneys. Thus, uremic pancreatopathy is frequently observed in patients with CRF, and serum pancreatic enzymes such as amylase are often elevated within three-fold,<sup>10-15</sup> due to the renal excretion impairment and subclinical pancreatic damage.<sup>11,12,14</sup>

Homocysteine (Hcy) is an endogenous sulfur-containing amino acid intermediate of the essential amino acid methionine and its metabolism depends upon folate, and vitamin B.<sup>16</sup> The kidney plays an important role in Hcy metabolism and clearance. When the GFR decreases, intrarenal Hcy metabolism will fall; however, Hcy levels increase as renal function declines and progresses to end-stage renal failure.<sup>17</sup>

Serum cystatin C (Cys-C), a non-glycosylated basic low molecular weight protein, has recently been suggested as an accurate marker of GFR with advantages over serum creatinine (Cr).<sup>18-20</sup> The increases of serum Hcy levels in humans with renal diseases are often reported<sup>19,21-24</sup> however, it has not been assessed in dogs with renal failure so far.

Based on the information, the study aimed to assess the serum gastrin, amylase, Hcy, and Cys-C concentrations in dogs with renal failure.

## MATERIAL and METHODS

### Dogs

In this study, 15 dogs with ARF and 15 dogs with CRF, of different breeds and both sexes, were used (Small Animal Clinic of Internal Medicine, Veterinary Teaching Hospital, Bursa Uludag University, Bursa - Türkiye). Also, based on the routine clinico-hemato-biochemistry profile, 15 healthy dogs served as controls.

### Diagnosis and staging of renal failure

ARF and CRF were diagnosed depending on the compatible clinical signs and laboratory test results, as suggested by the International Renal Interest Society (IRIS).<sup>3,25</sup> Stages of renal failure were categorized based on the severity of azotemia (serum

BUN or urea, and Cr levels), and stages III and IV were selected for this study. Dogs with exclusively prerenal or postrenal azotemia were excluded from the study.

### Data Collection and Analysis

After the routine physical examination, venous blood samples were drawn in vacutainer test tubes with or without EDTA for complete blood count examination (HM5 VetScan, Abaxis) and biochemical examinations. Serum BUN, Cr, total protein, and albumin levels were measured by Reflatron (Boehringer Mannheim, GmbH, Germany). Gastrin and amylase concentrations in serum samples were determined using the radioimmunoassay technique. Serum cystatin C and Hcy concentrations were determined using the Behring nephelometric system (Dade Behring, Marburg, GmbH) and Fluorescence Polarization Immunoassay (FPIA) (IMx system, Abbott Diagnostic Division), as suggested by Sigit et al.<sup>26</sup> and Almy et al.<sup>18</sup> respectively. Lower limits for detection of Hcy and cystatine concentration were 2 mmol/L and <0.24 mg/L, respectively.

Extra blood samples were not collected for biomarker analysis, meaning that only blood samples that were collected for diagnostic procedures were used in this study. All examinations were carried out in animal welfare and within the hospital working discipline. Thus, an ethics report was not needed.

### Statistical Analysis

All parameters were compared by one-way analysis of variance (ANOVA). Pearson correlation was performed between the serum biomarkers. Analysis was performed with the use of the SPSS 2.0 for Windows statistical software package (GmbH, Germany). *P*-values less than 0.05 were considered significant.

## RESULTS

Of the 45 dogs studied, 24 were male (7 intact), and 21 were female (9 intact). The mean age was  $7.1 \pm 2.3$  years (range 1.5 to 15 years) and body weight was  $10.1 \pm 4.0$  kg (range, 6.5-27 kg). In dogs with renal failure (n=30), breed distribution included Terrier (n=5), Boxer (n=5), Rottweiler (n=4), Doberman (n=2), Irish Setter (n=2), Cocker Spaniel (n=2), Golden Retriever (n=1) and mixed breed (n=9), while the control group (n=15) consisted of Terrier (n=4), Boxer (n=3), Rottweiler (n=3), Doberman (n=2) and Mixed breed (n=3). There are minor differences in vital clinical signs among the dogs studied (data not shown). Also, the results of routine diagnostic parameters were not given here because this study focused on the potential biomarkers that have not yet been comprehensively investigated in dogs. Hct value was significantly lower ( $p < 0.01$ ) in dogs with CRF, compared to other dogs (Table 1).

**Table 1.** Serum levels of selected hematobiochemical parameters and potential renal injury markers in dogs with acute (ARF) and chronic renal failure (CRF).

Parameters	Control Dogs Mean ± SE	Dogs with ARF Mean ± SE	Dogs with CRF Mean ± SE
Hematocrit (%)	39.3 ± 3.4 <sup>a</sup>	38.3 ± 4.5 <sup>a</sup>	27 ± 2.3 <sup>b**</sup>
Total protein (mg/dL)	7.2±1.6 <sup>a</sup>	8.3±2.1 <sup>a</sup>	5.3±0.9 <sup>a</sup>
Albumin (mg/dL)	3.5±0.5 <sup>a</sup>	3.7±1.2 <sup>ab</sup>	2.1±0.7 <sup>b**</sup>
BUN (mg/dL)	26 ± 1.3 <sup>a</sup>	161 ± 11.2 <sup>b***</sup>	288 ± 17.4 <sup>c***#****</sup>
Creatinine (mg/dL)	0.75 ± 0.04 <sup>a</sup>	2.30 ± 0.36 <sup>b**</sup>	6.87 ± 0.73 <sup>c***#****</sup>
Gastrin (pg/mL)	18 ± 3.8 <sup>a</sup>	11.4 ± 1.8 <sup>a</sup>	274.9 ± 87.3 <sup>b***#****</sup>
Amylase (U/L)	1129 ± 87 <sup>a</sup>	1575 ± 200 <sup>b***</sup>	1563 ± 299 <sup>b***</sup>
Cystatin C (mg/L)	< 0.24 <sup>a</sup>	0.4±0.1 <sup>b**</sup>	0.8±0.1 <sup>c***#****</sup>
Homocysteine (µmol/L)	10.1±2.4 <sup>a</sup>	13.5±5.5 <sup>a</sup>	41.4±4.4 <sup>b***#****</sup>

BUN: Blood urea nitrogen

a, b and c: Differences between different letters on the same line were found to be statistically significant at least  $p < 0.05$ .

\*\* $p < 0.01$  \*\*\* $p < 0.001$  # compared to the control group

Total protein concentration was lower but not statistically significant in dogs with CRF compared to the other groups. There was a significant difference in serum albumin between dogs with CRF and controls ( $p < 0.01$ ). Urea levels in dogs with ARF and CRF were much higher than in control dogs ( $p < 0.001$ ). Likewise, serum Cr values in dogs with renal failure were significantly higher ( $p < 0.001$ ) than those of control dogs.

Serum Cys-C levels increased in dogs with renal failure, compared to control dogs ( $p < 0.001$ ). These parameters were higher in CRF than in ARF dogs ( $p < 0.001$ ). Mean serum gastrin, Hcy, and amylase concentrations did not differ significantly between dogs with ARF and controls but were significantly higher ( $p < 0.01-0.001$ ) in dogs with CRF compared to others.

A positive correlation was found between serum creatinine and gastrin ( $r = 0.68$ ;  $p < 0.05$ ), Hcy ( $r = 0.71$ ;  $p < 0.05$ ), and cystatin ( $r = 0.72$ ;  $p < 0.05$ ) and between serum urea and Hcy ( $r = 0.87$ ;  $p < 0.05$ ) and cystatin ( $r = 0.66$ ;  $p < 0.05$ ) but was not found between serum Hcy and albumin concentrations in dogs. Serum Hcy and cysteine concentrations were significantly correlated ( $r = 0.67$ ;  $p < 0.05$ ).

## DISCUSSION

This study focused on, instead of well-known clinical and pathological findings of renal failure, whether serum gastrin, amylase, Hcy, and cystatin could be used to show the presence of renal injury and its severity in dogs. Our results showed that serum cystatin was superior to discriminate CRF from ARF and serum gastrin, amylase, and Hcy may increase regardless of the severity of the renal failure.

ARF is a syndrome characterized by an abrupt decline in renal function that occurs over hours to days, whereas CRF is marked by a slowly progressive deterioration in renal function over months to years.<sup>1</sup> Therefore, this study observed increases in serum urea and Cr values in dogs with CRF rather than dogs with ARF, indicating impaired GFR in parallel to the

severity of renal failure in dogs studied. In general, the increase of Cr and urea is stable in CRF, whereas these values progressively increase in ARF.<sup>1,27,28</sup> It is well known that hydration status can affect serum urea and Cr levels, so measurements of serum proteins in conjunctive with Hct value are suggested. There are no statistical differences in Hct values between healthy dogs and dogs with ARF. This was incompatible with a general statement that Hct values are generally normal or increase in dogs with ARF, but it decreases due to impaired erythropoiesis in dogs with CRF.<sup>17</sup>

In this study, serum gastrin levels were found to be higher in CRF dogs compared to ARF dogs. Observed mean serum gastrin level (247 pg/ml; 24.7 ng/dl) in dogs with CRF was higher than the results of a recent study (10.5 ng/dl).<sup>3</sup> This may be due to the differences in disease severity and measurements of gastrin between the two studies. The increase in gastrin levels (hypergastrinemia) might be due to a combined effect of impaired renal catabolism of gastrin and overproduction of gastrin associated with hypochlorhydria.<sup>6</sup> It was reported to be a slight increase in serum pancreatic enzyme during chronic renal pathology in humans.<sup>11,12</sup> Results vary with regard to the upper limits of serum amylase seen in patients with renal failure and very little has been reported with patients with renal insufficiency not yet requiring dialysis.<sup>15</sup> It is possible that in these patients together with the renal excretion impairment there could also be some subclinical pancreatic damage.<sup>14</sup>

In this study, increases in serum gastrin and amylase values are accompanied by increasing in serum Cr and urea values, indicating that both elevations may be effected by reducing GFR in dogs. The correlation between serum gastrin and severity of renal damage could be supported by the earlier studies.<sup>6,29,30</sup> We found that mean serum Hcy levels were 10.1 mmol/L, 13.5 mmol/L, and 41.4 mmol/L in dogs with healthy, ARF and CRF, respectively. In the present study, higher level of Hcy measured in the dogs with CRF was considered to be classified as an intermediate hyperhomocysteinemia, as defined in humans.<sup>21</sup> In

parallel to our observation, Suliman et al.<sup>23</sup> reported that almost all CRF patients had plasma concentrations of Hcy that were elevated 3 to 4 times above normal. It was reported that serum Hcy levels increased in dogs with CKD but there was not statistical difference between the CKD stages. In the present study, similar to a previous study, serum Hcy levels showed significant difference between healthy control and CRF but not between ARF and CRF dogs.<sup>31</sup> There is much evidence to show that the presence of moderate hyperhomocysteinemia is an independent risk for atherosclerosis and atherothrombosis in humans with or without renal failure.<sup>22,23,32-34</sup> Thus, dogs with CRF may be better if they are examined for development or presence of cardiovascular diseases. The increase in Hcy concentration was statistically significant in dogs with CRF ( $p<0.001$ ) but not significant in dogs with ARF, indicating that the Hcy value might have increased only in dogs with CRF. Recently, human studies suggested that increased Hcy concentration was determined in patients with cardiovascular problems due to CRF.<sup>24,32,34</sup> Decreased re-methylation is also responsible for increasing plasma Hcy in uremic renal failure.<sup>21,35</sup> On the basis of these reports, a possible reason for increasing Hcy in the serum of our dogs may be altered transmethylation reaction due to impaired renal functions leading to uremic syndrome. Van Guldener and Robinson<sup>36</sup> reported that proposed mechanisms included reduced renal elimination of Hcy and impaired nonrenal disposal, possibly because of inhibition of crucial enzymes in the methionine-Hcy metabolism by the uremic patients.

GFR estimated by cystatin and Cr levels are independent determinants of Hcy in CRF patients.<sup>19,37</sup> In humans, plasma Hcy is not only correlated to serum Cr as a result of renal function but also as a result of the relationship between Hcy production and creatine-creatinine synthesis.<sup>37</sup> Parallely, we found a positive correlation between serum Hcy and Cr concentrations, and also between serum Hcy and cystatin in dogs with CRF. Hcy levels are elevated in patients with impaired renal function, in whom plasma concentration seems to be inversely correlated to GFR.<sup>24,26,32</sup> In accordance with these reports, we found that serum Hcy increased in parallel to increasing serum urea, Cr and cystatin in dogs with ARF and CRF. In a recent study, it was reported that cats with CKD had significantly higher Hcy concentrations than cats at risk. The concentration of Hcy was higher in moderate-severe CKD than in mild CKD and correlated moderately with serum creatinine.

There are some limitations in this study. Firstly, symmetric dimethylarginine (SDMA) most commonly used as an early renal injury marker could have been measured in the presented study. The dogs studied

were already in the symptomatic phase of the renal failure, thus it was thought that SDMA analysis might not be necessary in those dogs. Secondly, it could be better if the renal anatomy was evaluated ultrasonographically.

In conclusion, the present study showed that serum gastrin, amylase, Hcy, and Cys-C concentrations may increase in dogs with renal failure, and increased Cys-C concentration could be a useful diagnostic parameter to differentiate between ARF and CRF in dogs. The clinician should keep in mind that these parameters may increase due to pre-renal azotemia, thus their results should be interpreted cautiously in clinical practice.

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