Urinary Transforming Growth Factor-β1 in Feline Chronic Renal Failure

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ABSTRACT. Transforming growth factor-β1 (TGF-β1), an inflammatory cytokine, plays a role in tissue fibrosis, such as glomerular sclerosis and tubulointerstitial fibrosis of the kidneys. In the present study, the urinary TGF-β1 level of cats diagnosed with chronic renal failure (CRF) was measured to investigate its relationship to the pathogenesis of feline CRF. Urinary TGF-β1 levels (TGF-β1/creatinine ratio) were significantly increased compared with healthy controls, whereas serum levels of TGF-β1 were not. These results indicate that TGF-β1 is expressed in the kidneys of CRF cats, and that it was reflected in the urinary TGF-β1 level. Therefore, TGF-β1 may play a role in feline CRF, and urinary TGF-β1 could be used as a clinical marker for renal fibrosis.

KEY WORDS: CRF, fibrosis, TGF-β1.

NOTE

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Chronic renal failure (CRF) is defined as a progressive, irreversible deterioration of kidney functions caused by underlying disease, aging, and the environment. Renal lesions are present in most CRF patients in which the progressive loss of parenchymal cells and irreversible fibrosis are observed [2, 8]. Neither preventative measures nor a cure for renal fibrosis have been discovered, and the treatment of CRF remains the alleviation of symptoms, even in human medicine.

Transforming growth factor-β1 (TGF-β1) is an inflammatory cytokine common to several species that plays a role in tissue fibrosis. It is released by parenchymal and infiltrating cells, stimulates the production of extracellular matrix (ECM) proteins and inhibits their degradation, and transdifferentiates epithelial cells into myofibroblasts through the expression of alpha-smooth muscle actin (α-SMA) [3]. Several studies in experimental animal models and human patients with renal diseases have pointed to a causal relationship between the overexpression of TGF-β1 and the onset of glomerular and tubulointerstitial fibrosis of the kidneys. Elevated renal TGF-β1 is correlated to the degree of interstitial fibrosis or glomerular sclerosis [13, 17, 18]. In addition, the urinary TGF-β1 level is also correlated to histological changes in the kidneys and renal TGF-β1 expression [6, 10], and is especially high in patients with membranous glomerulonephritis [7] and diabetic nephropathy [9, 15]. On the other hand, the biological neutralization of TGF-β1 prevents the increased production of ECM in glomeruli [1]. These results indicate that the urinary TGF-β1 level may be clinically useful as a marker of renal fibrosis and as a new parameter that is informative, but less invasive and of lower risk in terms of determination compared with renal biopsies [3].

Feline CRF is a common disease that is similar to human CRF in some respects, such as its various underlying causes and the resultant renal fibrosis, accumulation of ECM, and proliferation of myofibroblasts in the kidneys [5, 14, 16]. Therefore, this indicates that TGF-β1 is a key factor in the pathogenesis of feline CRF as well as humans and other animals. In the present study, the urinary TGF-β1 level was measured in CRF cats to investigate its possible use as a clinical marker of feline CRF and its relationship to disease development and progression.

Cats diagnosed with chronic renal failure (CRF), acute renal failure (ARF), or diabetes mellitus (DM) were selected for this study from cats referred to Veterinary Medical Center of the University of Tokyo by other practical veterinarians from June, 2003, to October, 2004. They were then divided into 5 groups, designated CRF, DM, CRF with DM, ARF, and controls. The diagnosis of CRF was made based on a persistent high creatinine concentration of ≥2.2 mg/dl and a decreased level of urine specific gravity (USG) of <1.030 [4]. The diagnosis of post-renal ARF was made based on little or no urine elimination, the existence of urine outflow obstruction, and a high blood urea nitrogen (BUN) concentration of ≥32 mg/dl [4]. Finally, the diagnosis of DM was made based on clinical signs, such as polyuria and polydipsia, persistent hyperglycemia with blood glucose ≥300 mg/dl, and glucosuria [12]. Healthy cats determined to be clinically normal by routine examination were used as controls.

For the measurement of TGF-β1, urine samples were obtained by pressured urination or bladder centesis and centrifuged at 1,500 rpm for 5 min. Serum samples were also obtained after centrifugation of blood samples at 3,000 rpm for 5 min in serum tubes. The urine and serum sample supernatants were then collected and frozen at −20°C until assay. The concentrations of TGF-β1 in the urine and serum were measured using a Multispecies TGF-β1 ELISA kit (BioSource International, Inc., Camarillo, CA). To normal-
The median urinary TGF-β1 levels were not significantly different between any other two groups (p>0.05). No significant differences were observed among the three groups using the Tukey-Kramer test (p=0.05).

In human medicine, diabetic nephropathy is a critical disease, and some markers must be examined to know its pre-clinical status. As a candidate clinical marker, an increase in the urinary TGF-β1 level with the histological findings of each kidney. In the present study, cats were selected based on abnormalities seen by blood chemical examination, so it was not known at which stage elevation of urinary TGF-β1 begins. Since the urinary TGF-β1 level reflects the degree of renal lesions [10, 11], it may increase in advance of clinical signs or the elevation of BUN and creatinine levels. Further investigation using a large number of cats, especially aged ones, is necessary to determine whether urinary TGF-β1 can be used as an early diagnostic marker of feline CRF.

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urate to pathogenesis similar to human diabetic nephropathy.

Renal biopsy is not an easy-to-perform or routine examination. It requires anesthesia to be performed under the best conditions. Since anesthesia and bleeding pose a higher risk for CRF cats, histological examination could not be performed on CRF patients in the present study. Therefore, the degree of renal fibrosis and TGF-β1 expression was not determined. To investigate the correlation between the urinary TGF-β1 level and renal lesions or TGF-β1 expression, it is necessary to develop an experimental CRF model for cats similar to naturally occurring feline CRF.

In conclusion, urinary TGF-β1 levels are higher in CRF cats and could be used as a clinical marker for feline CRF.

REFERENCES