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Cystatin C as a marker and its clinical importance

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Abstract
Cystatin C is a non glycosylated neuroendocrine protein having isoelectric pH of 9.3, encoded by CST3 gene. It is a low molecular weight protein approximately 13.3 kilodaltons consisting 120 amino acids and is removed from the bloodstream by glomerular filtration in the kidneys which can be used as a biochemical marker for proximal tubular damage superior to serum creatinine (sCr). Increased levels of CysC are linked with the risk of death, several types of cardiovascular disease and healthy aging. sCysC is a better glomerular filtration rate marker than sCr for its early detection in incipient diabetic nephropathy. Concentration of cystatin C is increased in patients with hypothyroidism and decreased in patients with hyperthyroidism with treatment. Individuals with untreated carcinomas and leukaemia had significantly higher sCysC concentrations compared to treated patients due to its antitumor effect. CysC regulates certain aspects of immune function because interleukin-10 controls CysC synthesis in response to inflammation.

Keywords: Cystatin C, diabetes, hypothyroidism, hyperthyroidism, leukaemia

Introduction
The livestock sector of India is one of the largest populations in the world and contributes the largest economy to the India. Different systemic diseases like kidney diseases, neuronal diseases and cardiovascular diseases are being emerged widely not only in medical but also in veterinary field. Proper diagnosis is the major problem to combat these diseases in animal. Chronic kidney disease (CKD) is an important emerging disease not only in human but also in animals [1]. So early detection and treatment of this disease is very important which increases the survival rate by preventing the additional renal damage [2]. Evaluation of kidney function is done by direct measurement of Glomerular Filtration rate (GFR), but it is very labour intensive and time consuming [3]. Indirect markers of GFR i.e. serum Creatinine (sCr) and blood Urea Nitrogen (BUN) can be easily measured but the only disadvantage is that they are influenced by non-renal factors, such as age, diet, hydration status and muscle mass [4].

To overcome this problem, an ideal endogenous marker should be evaluated to assay the kidney function. Use of serum Cystatin C (CysC) as a marker of GFR is well documented and some authors have suggested that it may be more accurate than sCr for this purpose [5]. CysC has a stable production rate and is removed from the blood circulation by glomerular filtration. In healthy individuals, CysC is completely reabsorbed and degraded in the tubules. A normal value for CysC in serum ranges from 0.8 to 1.2 mg/L and in patients with renal tubular disorders may be raised as high as 2 to 5 times as the normal values. CysC is an endogenous renal marker and is not affected by age, sex, nutrition and other factors. Serum CysC is considered to be a more sensitive marker than Cr in patients with moderate decrease in GFR [6]. CysC, having many properties like constant production and plasma concentration in the absence of GFR variation, low intra individual variability, no plasma protein binding, no tubular secretion, no tubular reabsorption without catabolism and renal clearance make it a suitable endogenous GFR marker [6].

Cystatin C, a low molecular weight protein approximately 13.3 kilodaltons, is removed from the bloodstream by glomerular filtration in the kidneys that can be used as a biochemical marker for proximal tubular damage superior to sCr. This can be used as new biological tool for other diseases like neuronal, cardiovascular and also different metabolic diseases in livestock sector. In human, the variation of CysC due to different biological factors (age, sex, body weight) was extensively studied but contradictory results were reported regarding the effect of age and body weight on sCysC in dogs. Plasma CysC was shown to be lower in adult dogs compared with younger and older dogs and lower in dogs with body weight <15 Kg

compared with heavier dogs. It is a non-glycosylated, neuroendocrine protein having isoelectric pH of 9.3, encoded by the CST3 gene, mainly measured in cerebrospinal fluid, followed by plasma, saliva, and urine which indicates its production in the central nervous system and catabolism by the kidney [7]. It is expressed virtually in all organs of the body which indicates CST3 is a housekeeping gene. It is a single chain polypeptide consisting of 120 amino acids characterized by a short alpha helix and a long alpha helix which lies across a large antiparallel, five stranded beta sheet with two disulfide bonds. This protein protects host tissue against destructive proteolysis by inhibiting the activity of cysteine proteinases. There are three divisions of inhibitory families which include type 1 Cystatins (stefins), type 2 Cystatins and the kininogens. The type 2 Cystatin proteins are a class of cysteine proteinase inhibitors that are mainly used as a biomarker for kidney function than serum creatinine based on the findings in both cross-sectional as well as longitudinal studies [8].

Renal disorder

The function of kidney is evaluated by glomerular filtration rate (GFR) which is assayed by measuring renal clearance value of different exogenous markers like Inulin and different isotopically labeled compounds including iothalamate, iodothalamate, chromium ethylenediamine tetra acetic acid (Cr-EDTA) and technetium diethylenetriamine pentaacetic acid (99mTcDTPA) [7]. Due to time-consuming and labor-intensive of these clearance tests, the measurement of indirect markers BUN and sCr is routinely used to estimate GFR but these are influenced by muscle mass, age, feeding status, sex and intra-individual variation. It is found that the level of sCysC is influenced by body composition [9]. It might predict the risk of developing chronic kidney disease, thereby indicates the state of 'preclinical' kidney dysfunction. It is also investigated that in the adjustment of medication dosages it acts as a marker for kidney function [10]. It has been reported that the level of sCysC of patients is altered in case of cancer [11] thyroid dysfunction [12] and glucocorticoid therapy in some situation. Its levels seem to be increased in HIV infection, which may or may not reflect actual renal dysfunction [13]. During pregnancy, the role of it to monitor GFR remains still controversial [14]. CysC is freely filtered through the glomerulus, reabsorbed, and catabolized in the tubules, as has been shown in rats. With normal renal function, CysC can be found in small quantities in the urine. With proximal tubular damage, uCysC increases. Urinary CysC was higher in patients with renal tubular damage compared with patients with proteinuria without tubular damage.

Acute Kidney Injury (AKI) is associated with high mortality. Therefore, early detection is critical to prevent further progression. Serum CysC concentration could detect development of AKI 1 or 2 days earlier than sCr concentration in intensive care patients with ≥2 predisposing factors of AKI. Interestingly, the uCysC concentration also may predict renal replacement requirement in patients initially diagnosed with nonoliguric acute tubular necrosis. In similar studies, CysC was as effective as or less sensitive than sCr in the detection of AKI. However, similar to sCr, CysC could not discriminate between CKD and AKI. The use of CysC to detect AKI must be evaluated in larger studies and with different types of AKI and that the prognostic value also must be determined [15].

[16] Evaluated cystatin C concentration as a marker of glomerular filtration rate in renal transplant recipients, and its correlation with creatinine-based glomerular filtration rate by urinary creatinine clearance, and the Cockroft-Gault and Modification of Diet in Renal Disease formulas. Their results show that serum cystatin C is a reliable marker for estimating glomerular filtration rate among renal transplant recipients. This test can determine the glomerular filtration rate of renal transplant recipients on follow-up.

Cardiovascular disorder

Increased levels of CysC are linked with the risk of death, several types of cardiovascular diseases (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) and healthy aging [17]. The basal metabolic rate may affect the level of CysC [18]. Its levels are decreased in atherosclerosis and aneurismal lesions of the aorta [19]. Chronic kidney disease is a known risk factor for ischemic heart disease. In contrast with sCr, CysC was associated with an increased risk of heart failure. Serum CysC tends to be a stronger predictor of mortality than sCr in elderly individuals with heart failure as well as in the wider elderly population. Because CysC is a proteinase inhibitor that plays an important role in tissue remodeling. A higher CysC concentration also could represent a compensatory mechanism in vascular injury.

Diabetes mellitus

It has been seen that sCysC is a better GFR marker than sCr for the early detection of incipient diabetic nephropathy [20]. Diabetic nephropathy is a common complication in human diabetes patients and is characterized by persistent albuminuria and an associated decrease in GFR. Moreover, the correlation between GFR measured with 51Cr-EDTA and sCysC ($r = 0.84$) significantly stronger compared with using estimated GFR ($r = 0.70$). However, others have reported that sCysC is equal to sCr as a GFR marker in micro and macroproteinuric diabetes patients.

Thyroid Function

The impact of thyroid dysfunction on sCysC was investigated. sCysC concentration is increased in patients with hypothyroidism and decreased in patients with hyperthyroidism with treatment [21]. In patients with hyperthyroidism, renal blood flow is stimulated, which causes increased GFR [22]. Serum creatinine concentration decreases, which masks patients with concurrent chronic kidney disease. Contrasting effects have been observed in patients with hypothyroidism. As sCysC was introduced as a new marker of kidney function, the impact of thyroid dysfunction on sCysC also was investigated. With treatment, sCysC concentration increased in patients with hypothyroidism and decreased in patients with hyperthyroidism. However, others did not observe higher or lower sCysC concentrations in patients with untreated hyper or hypothyroidism, respectively. When considering sCysC concentrations in patients with hyperthyroidism, GFR is underestimated and in patients with hypothyroidism, GFR is overestimated. Den Hollander suggested that there is increased or decreased production of CysC in hyper and hypothyroidism, respectively, because of the influence of the thyroid state on general metabolism.

Serum concentrations of CysC and transforming growth factor β1 (TGF-β1) were significantly higher in patients with hyperthyroidism, and a positive correlation among sCysC, thyroid hormones. After treatment, sCysC and TGF-β1

decreased. In vitro findings have suggested an increase in TGF-β1 concentrations in hyperthyroidism and a stimulatory effect of thyroid hormones and TGF-β1 on CysC production [23].

Cancer

It has been investigated that individuals with untreated carcinomas and leukemia had significantly higher sCysC concentrations compared to treated patients due to its antitumor effect [24]. Renal disease has high prevalence of neoplasia. Decreased regulation by Cystatins is responsible for increased cysteine protease activity in tumor cells. Cystatin C has 2 antitumor effects. First, it is a major inhibitor of the cathepsins, enzymes that cause degradation of basal membranes by tumor cells. Therefore, CysC suppresses the metastastic process. Second, CysC inhibits TGF-β and the TGF-β signaling pathway. The specific role of CysC in oncogenesis has not yet been elucidated. However, individuals with untreated carcinomas and leukemia had significantly higher sCysC concentrations compared with patients after treatment. However, other studies did not find a difference in sCysC concentrations between patients with malignancy and a healthy control group [7].

Inflammation

In vitro, CysC regulates certain aspects of immune function because IL-10 controls CysC synthesis in response to inflammation [25]. Several reports have shown a good correlation between sCysC and other inflammatory markers, but these studies were performed in populations with either cardiovascular or renal impairment, which can cause bias. It has been studied that Dexamethasone cause a dose-dependent increase in CysC secretion in vitro; in vivo, sCysC is influenced by prednisolone administration.

CysC in small animal medicine

The role of Cystatin C in small animal medicine has been emerged recently with wide range application in dog and cat. It has been shown that there is no influence of inflammation on sCysC in dogs [26]. In critically ill dogs, sCysC concentrations were significantly higher in dogs in shock compared to healthy dogs. But this result was not observed in multiple-trauma dogs [27]. A correlation between GFR and sCysC was performed to identify the most appropriate marker for screening for renal damage in dogs with babesiosis [28]. This protein can be used as marker in dogs with visceral leishmaniasis, characterized by immune-complex disposition and glomerular injury. In cat, increased or decreased sCysC concentrations are influenced with hyper and hypothyroidism. The effect of neoplasia on sCysC in small animals needs to be evaluated due to its antitumor activity.

Serum cystatin C has been evaluated as a GFR marker in dogs using commercially available particle-enhanced turbidimetric immunoassay (PETIA), particle enhanced nephelometric immunoassay (PENIA) and ELISA methods [29]. Available literature has validated PETIA1 for measuring canine uCysC in healthy dogs, dogs with renal impairment and dogs with non-renal disease. The assay was linear and precise and the uCysC/uCr ratio was significantly higher in dogs with renal disease compared with healthy dogs and dogs with non-renal disease. In cats, PENIA2 was validated for measuring feline uCysC and a significant difference in uCysC/uCr ratio between healthy cats and cats with CKD was observed. Although the results for uCysC seem promising in both dogs and cats, additional studies are required. First, uCysC has not yet been investigated as a marker of early renal damage. Second, canine and feline purified CysC were not available and therefore, the accuracy of the method could not be evaluated.

Conclusions

Cys C may be regarded as a suitable biochemical marker for diagnosis of renal and other systemic diseases not only in humans but also in veterinary subjects. But the validation in respect with analytical, biological and clinical testing is still to be needed for widespread use. A thorough analytical validation of the nephelometric and turbidimetric assays for determining CysC in serum and urine in both cats and dogs is needed for further clinical application. Plasma Cystatin C concentration is an accurate GFR marker in cirrhotic patients. Plasma creatinine concentration and calculated creatinine clearance are of no practical value, as their reference values vary with the severity of the liver disease. Cystatin C may help clinicians in diagnosing early kidney damage more effectively than by measuring creatinine levels alone.

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