

Mini Review

Cystatin C: A new biochemical marker in livestock sector

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ABSTRACT

The livestock sector contributes largely to the economy of India. Different systemic diseases like renal diseases, neurological and cardiovascular diseases cause huge loss in production and productive potential of livestock in India, which is considered as a major concern for both small and large ruminants. Early detection of diseases is essential to combat the economic loss. An efficient biochemical marker can be developed which would provide more specific, sensitive and reliable measurement of functions of different organs. Determination of endogenous marker Cystatin C may fulfill the above need which can provide a detection platform not only for Kidney function but also for assaying other organs' function. Cystatin C is a low molecular weight protein which is removed from the bloodstream by glomerular filtration in the kidneys. Thus, it may act as a potential biological tool in diagnosis of renal and other systemic diseases in livestock. This mini-review focuses on the Cystatin C and its clinical importance which can be extensively employed in the livestock sector.

KEYWORDS

Biochemical marker, Cystatin C, Glomerular filtration, Livestock sector

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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 human sector but also in small animal. Proper diagnosis is the major problem to combat these diseases in veterinary sector. Chronic kidney disease (CKD) is an important emerging disease not only in human being but also in veterinary sector (Coresh et al., 2007). Early detection and treatment of this disease is very important which increases the survival time by preventing the additional renal damage (Boyd et al., 2008). Evaluation of kidney function is done by direct measurement of Glomerular Filtration rate (GFR), but it is very labor-intensive and time-consuming (Paepe and Daminet, 2013). Indirect markers of GFR i.e. serum creatinine and blood urea nitrogen [BUN] can be easily measured but the only disadvantage is that they are influenced by nonrenal factors, such as age, diet, hydration status, and muscle mass (Braun and Lefebvre, 2008). To overcome this problem, an ideal endogenous marker should be evaluated to assay the kidney function. Cystatin C, 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 no extrarenal clearance make it a suitable endogenous GFR marker (Seronie-Vivien et al., 2008). Cystatin C, a low molecular weight (approximately 13.3 kilodaltons) protein, 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] (Conti et al., 2006). This can be used as new biological tool for other diseases like neuronal, cardiovascular and also different metabolic diseases in livestock sector. There should be adequate information regarding the structure of cystatin C and its potential role in the clinical veterinary medicine. So the objective of this article is to describe all the above characteristics which would provide a good platform for reviewers to understand the clinical role of cystatin C which can lead it to a precise biochemical marker in livestock sector.

CYSTATIN C

It is a non glycosylated, neuroendocrine basic protein (isoelectric pH 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

(Ghys et al., 2014). It is expressed virtually in all organs of the body which indicates CST3 is a housekeeping gene. It is single chain polypeptide (molecular weight 13.260 kDa) constituted 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 (Bobek and Levine, 1992). There are three divisions of inhibitory families which includes 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 (Premaratne et al., 2008). A better correlation between the reciprocal of serum CysC and GFR makes it as a potential marker for GFR as compared to other the serum low molecular weight proteins such as beta-2 microglobulin, retinol binding protein and factor D (Grubb et al., 1985). The mechanisms of occurrence renal dysfunction, inflammation, atherogenesis, and cardiovascular events linked with CysC are shown in (Figure 1).

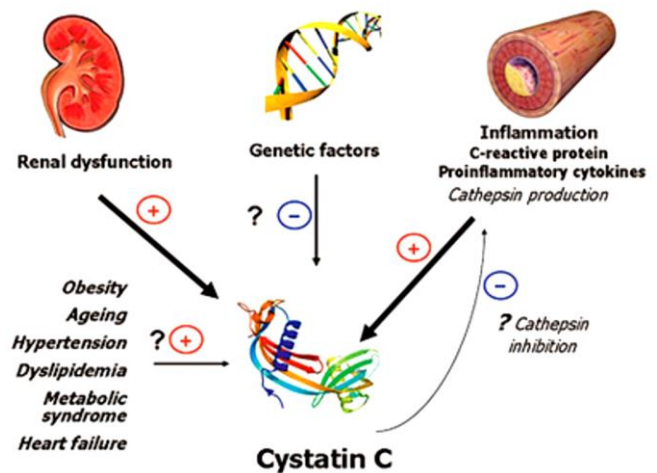


Figure 1: Mechanisms linked with CysC leading to renal dysfunction, inflammation, atherogenesis, and cardiovascular events. Adopted from Taglieri et al (2009).

CysC AND GFR

The function of kidney is evaluated by GFR which is assayed by measuring renal clearance value of different exogenous markers like Inulin different isotopically labeled compounds including iothalamate, iodothalamate, chromium ethylenediamine tetraacetic acid (Cr-EDTA) and technetium diethylenetriamine pentaacetic acid ($^{99m}\text{TcDTPA}$) (Ghys et al., 2014). 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 intraindividual variation. The reciprocal of sCysC correlates more closely with GFR, as measured by exogenous clearance tests, than the reciprocal of sCr has been described in humans in several studies. It is found that the level of sCysC is influenced by body composition (Shlipak, 2007). It might predict the risk of developing CKD, thereby indicates the state of 'preclinical' kidney dysfunction (Shlipak et al., 2006). It is also investigated that in the adjustment of medication dosages it acts as a marker for kidney function (Hermida and Tutor, 2006). It has been reported that the level of sCysC of patients is altered in case of cancer (Nakai et al., 2008), thyroid dysfunction (Manetti et al., 2005) and glucocorticoid therapy in some situation (Risch et al., 2001). Its levels seem to be increased in HIV infection, which may or may not reflect actual renal dysfunction (Jaroszewicz et al., 2006). During pregnancy, the role of it to monitor GFR remains still controversial (Akbari et al., 2005). The CysC can be eliminated other than the kidney route indicating worsening of GFR (Sjostrom et al., 2005).

CysC IN CARDIOVASCULAR DISEASE

Increased levels of CysC are linked with the risk of death, several types of cardiovascular disease (including myocardial infarction, stroke, heart failure, peripheral arterial disease and metabolic syndrome) and healthy aging (Djousse et al., 2008). The basal metabolic rate may affect the level of CysC (Delanaye et al., 2008). Its levels are decreased in atherosclerosis and aneurismal lesions of the aorta (Abisi et al., 2007).

CysC IN NEUROLOGIC DISORDERS

It has been reported that CysC levels are higher in Alzheimer's disease (Chuo et al., 2007). The role of cysC in multiple sclerosis and other demyelinating diseases remains controversial (Del Boccio et al., 2007).

CysC IN OTHER CLINICAL CONDITIONS

DIABETES MELLITUS

It has been seen that sCysC is a better GFR marker than sCr for the early detection of incipient diabetic nephropathy (Mussap et al., 2002)

ACUTE KIDNEY INJURY (AKI)

The development of AKI can be detected by measuring Serum CysC concentration 2 days earlier than sCr

concentration in intensive care patients with ≥ 2 predisposing factors of AKI (Herget-Rosenthal et al., 2004a).

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 (Manetti et al., 2005).

CARDIOVASCULAR RISK

It has been shown that CysC was associated more with an increased risk of heart failure in contrast with sCr (Shlipak et al., 2005). It tends to be a stronger predictor of mortality than sCr in elderly individuals with heart failure.

CANCER

It was investigated that individuals with untreated carcinomas and leukemia had significantly higher sCysC concentrations compared with patients after treatment (Demirtas et al., 2006) due to its antitumor effect (Sokol et al., 2005).

INFLAMMATION

As interleukin-10 controls the synthesis of CysC in response to inflammation in vitro, it regulates certain aspects of immune function (Xu et al., 2011). CysC secretion is increased on administration of dexamethasone in vitro and it is influenced by administration of prednisolone in vivo (Bokenkamp et al., 2002).

Cys C 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 (Wehner et al., 2008). In a study comprising 10 volume-depleted dogs and 1 dog with AKI, a weaker correlation between sCysC and GFR than sCr and GFR was observed (Almy et al., 2002). In critically ill dogs, sCysC concentrations were significantly higher in dogs in shock compared with healthy dogs, but this result was not observed in multiple-trauma dogs (Pasa et al., 2008). A correlation between GFR and sCysC was performed to identify the most appropriate marker for screening for renal damage in dogs with babesiosis (de Scally et al., 2006). 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.

BIOLOGICAL VARIATION OF CYS C

In human, the variation of Cys C 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 ([Braun et al., 2002](#)). [Wehner et al. \(2008\)](#) included 99 healthy dogs with an equal sex distribution (52 female, 47 male dogs) and a wide range in age and body weight (3 m–13 years; 5–42 Kg). In contrast, the study of Pagitz was limited by including only 24 healthy dogs (16 female and 8 male) with an age range of 10–97 months ([Pagitz et al., 2007](#)). So, additional studies in a larger number of healthy dogs, preferably in which GFR is measured, are required. The effect of meal on plasma CysC concentration was studied in dog. The concentration of plasma CysC showed a dramatic decrease during the first hour after a meal and this decrease lasted for 9 h and then returned to baseline after 12 h ([Braun et al., 2002](#)) in contrast to plasma Cr concentration, which increases in dogs during the first 12 h after a meal ([Braun et al., 2003](#)). The increased clearance of CysC could explain its decreased concentration after a meal because its concentration is mainly determined by GFR ([Gislefoss et al., 2009](#)).

LABORATORY MEASUREMENT

Currently, measurement of CysC is not available in veterinary sector. It can be measured in a random sample of serum using immunoassays such as nephelometry or particle enhanced turbidimetry ([Croda Todd et al., 2007](#)). In case of human a fully automated particle-enhanced turbidimetric immuno-assay (PETIA) for CysC was developed and validated in serum and urine ([Sohrabian et al., 2012](#)). After a few years later, another assay *i.e.*, a particle-enhanced nephelometric immuno-assay (PENIA) was validated in serum and urine ([Herget-Rosenthal et al., 2004b](#)). The major difference between these two methods is that PENIA can only be used with a specialized automated immunonephelometer, whereas PETIA can be used with several analyzers, including the Cobas Fara analyzer ([Garrido et al., 2002](#)), Hitachi analyzer ([Al-Turkmani et al., 2008](#)), Cobas 6000 analyzer and Abbott Architect ci8200. Newer devices are available but are limited in livestock due to its high cost.

CONCLUSION

Cys C may be regarded as a suitable biochemical marker for diagnosis of renal and other systemic diseases not only in human sector but also in livestock sector. 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. This review provides the significant information about CysC which would provide an important biological tool for diagnosis of various diseases in livestock sector in recent advances.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with any other people or organizations in any financial or personal relationship.

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