Clinical significance of cystatin C in acute coronary syndromes: is it really more than a marker of renal function?

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Serum cystatin C (Cys-C) levels perform better than other markers of renal function as indicator of cardiovascular outcome both in population-based studies and in patients with non-ST-elevation acute coronary syndrome (NSTEMI). Whether the relation between elevated serum Cys-C levels and risk of a worse cardiovascular prognosis reflects a more precise measurement of renal function or an association with non-renal factors such as inflammation is a matter still poorly defined. In a prospective, multicenter study our group evaluated the time course of serum Cys-C levels in 222 patients over the first 6 weeks after an episode of NSTEMI and a successful percutaneous revascularization. We observed that Cys-C levels slightly but significantly increased from the admission to 6-week samples (7.1 to 7.8 mg/dL, p <0.0001), contrary to high sensitivity C Reactive Protein (hsCRP), N-terminal portion of the proBNP peptide (NT-proBNP), and Interleukin 6 (IL-6) levels which significantly decreased in the same period. Cys-C levels were not different in patients with or without elevated troponin (c-TnT), whereas the other inflammatory and biomechanical markers showed higher values in patients with versus those without increased c-TnT. Cys-C was highly correlated with estimated glomerular filtration rate both in ACS and 6-week samples. In conclusion, our data seem to contradict the hypothesis that inflammation is a determinant of the Cys-C levels because they did not show the typical pattern of an acute-phase reactant and secondly they were independent from myocardial necrosis diagnosed by c-TnT levels. Moreover, our results show that Cys-C remains a reliable marker of renal function also during ACS because is not influenced by myocardial necrosis or by acute left ventricular dysfunction, as detected by increased NT-proBNP values.

Keywords: cystatin C; inflammatory prognostic markers; non-ST-elevation acute coronary syndrome

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Introduction

Besides serum creatinine, the standard biomarker adopted in the international guidelines to diagnose and classify kidney disease in epidemiological studies as well
as in clinical practice, cystatin-C (Cys-C) has recently gained increasing relevance as an easy, relatively inexpensive alternative biomarker to predict incident kidney dysfunction and to classify kidney disease [1,2]. Moreover, recent population-based studies documented that even mild elevations in Cys-C predicted risk of all-cause and cardiovascular mortality, heart failure, and end stage renal disease (ESRD) better than glomerular filtration rate (GFR) based on serum creatinine levels [3,4].

Serum Cys-C level as single measurement has been proven to be a good independent prognostic indicator of early and long-term all-cause and cardiovascular mortality also in patients with suspected or confirmed non-ST elevation acute coronary syndromes (NSTE-ACS) in addition to the risk stratification provided by traditional risk factors and more reliably than other markers of renal function [4,5,7]. However, no data are available until now on the in-hospital and post discharge time course of Cys-C level in patients with an episode of acute coronary syndrome (ACS).

The purpose of our paper was to assess whether Cys-C in the setting of ACS has a prognostic value similar to other inflammatory markers such as C-reactive protein (CRP) or remains a more refined marker of renal function not related to myocardial ischemia.

Cystatin-C as a marker of renal function

Thanks to its prevalent glomerular filtration, complete reabsorption in the proximal tubule, and lack of tubular secretion, plasma Cys-C concentrations depend almost completely on GFR. Although plasma Cys-C concentrations have been shown to be partially influenced by age, body mass index, sex, smoking habits, and high concentration of CRP, recent studies have demonstrated that a cystatin based formula including such variables performed better than serum creatinine for the estimation of GFR [1,2]. In a pooled post hoc analysis, participants in the Multi-Ethnic Study of Atherosclerosis (MESA) and in the Cardiovascular Health Study (CHS) were classified in 4 categories by Cys-C-based and creatinine-based GFR: no CKD, CKD by creatinine only, CKD by cystatin C only, and CKD by both [8]. The results of this analysis demonstrated that persons without and those with CKD (79% and 8% of participants respectively) identified by both equations had respectively the lowest and the highest risk profile for all-cause mortality, cardiovascular events, heart and kidney failure. A post hoc analysis of a large cohort of patients older than 65 years recruited in the CHS documented that the adjusted HR for all-cause and cardiovascular mortality at a median follow-up of 7.4 years increased linearly from the lowest to the highest concentrations of Cys-C [9]. A notable result of the study was that, within each quintile of serum creatinine, increasing levels of Cys-C were directly associated to a worse outcome. Furthermore, a subanalysis of the study,
evaluating the association between Cys-C, creatinine, GFR calculated by means of the Modification of Diet in Renal Disease (MDRD) equation and risk for incident heart failure (HF), showed that at a median follow-up of 8.3 years high concentrations of Cys-C predicted risk of developing HF more accurately than creatinine and eGFR. Finally, in a large population-based longitudinal study, participants were classified in 8 CKD groups defined by Cys-C or creatinine base GFR and ACR\textsuperscript{[10]}. Again, patients without and those with CKD defined by all three markers had respectively the lowest and the highest risk profile for death and ESRD over a median follow-up of 4.6 years. Among persons without CKD by creatinine only, the other two markers identified subgroups of patients with renal failure at increased risk for both outcomes.

All together these recent studies suggest that in a multi-marker approach to classify CKD the addition of Cys-C to traditional creatinine can improve diagnosis of renal failure and refine risk stratification for mortality, cardiovascular events, stroke and ESRD.

**Is Cystatin-C also an inflammatory Marker?**

Many studies have documented that several pathologic events occurring during initiation, progression, and complication phases of atherosclerosis are expression of a modified turnover of the extracellular matrix of the vascular wall and of the fibrous cap of the plaque \textsuperscript{[11]}. Different families of proteolytic enzymes (matrix metalloproteinases, serine and cysteine proteases), coming from inflammatory mononuclear leukocytes or activated smooth muscle cells (SMC), have been involved in the long-standing process of damage and remodelling of the extracellular matrix \textsuperscript{[12]}. Macrophages and activated T-cells, the most abundant inflammatory cells in the plaque, synergistically work to weaken the fibrous cap either augmenting the breakdown of collagen or inhibiting the synthesis of new extracellular matrix throughout multiple proteolytic enzymes and inflammatory mediators. In such inflammatory cells of the human atheroma and at sites of internal elastic lamina immunohistochemical studies have permitted detection and characterization of novel lysosomal cysteine proteases, such as cathepsins S and K. Blood monocytes and SMC of normal human vessel wall do not express cysteine protease activity, but incubation of these cells with inflammatory cytokines induces significant expression and secretion of cathepsins S and K \textsuperscript{[12]}. These findings suggest that a similar process may occur in the development of the atherosclerotic plaque and its complications.

Despite the wide range of systemic diseases where multiple functions of Cys-C related and unrelated to its protease inhibitory activity have been implicated, its pathophysiologic role and clinical relevance is still poorly defined. The hypothesis attributing to Cys-C an endogenous competitive inhibitory activity of lysosomal
cysteine proteases has many drawbacks. First, relatively low level of Cys-C has been demonstrated in human atherosclerotic lesions, whereas normal arteries express abundant Cys-C in SMC and endothelial cells [13]. Second, in contrast to the response of normal human monocytes and SMC under incubation with different inflammatory cytokines, it has been observed that these cells under the same conditions reduce or do not affect at all Cys-C expression [13]. However, some experimental observations indicate that expression of Cys-C may be tightly regulated by external factors, raising the clinical hope of designing strategies to reduce or promote Cys-C expression as a treatment in diverse pathologic conditions [14]. These observations indicate that inflammatory stimuli differentially affect the expression of lysosomal proteases and their endogenous inhibitors in the various cells of the arterial wall, but do not support the hypothetical elastolytic protease inhibitor activity of Cys-C.

On the clinical scenario, the conflicting results of various population-based studies aimed to document the hypothesis of Cys-C as a biomarker of inflammation and its prognostic cardiovascular importance reflect the above mentioned experimental uncertainties [9, 15]. In the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, originally designed to evaluate the impact of albuminuria on cardiovascular and renal diseases, Knight et al found that not only older age, male gender, smoking, and weight but also elevated CRP levels were positively correlated to higher serum Cys-C level independently of their effects on renal function [16]. Specifically, the direct association between serum Cys-C level and CRP remained significant after adjusting for other confounders such as obesity and smoking. In a post hoc analysis of the Heart and Soul Study, a prospective cohort study originally designed to examine the influence of psychosocial factors on coronary artery disease progression, Singh et al [17] found that the highest quartile of Cys-C was linearly and significantly associated with serum CRP and fibrinogen after multivariate adjustment. However, this association was no longer significant after correction for creatinine-based estimated renal function, whereas the lowest quartile of eGFR was linearly correlated with each higher inflammatory biomarkers concentrations only among persons with eGFR <60 ml/min/1.73 m². The different results of the 2 studies may be partially explicated by the important differences in the population characteristics.

In conclusion, there are no epidemiological or randomized studies, based on direct measures of GFR as a predictor of cardiovascular outcome, evaluating whether the association between elevated serum Cys-C concentrations and risk of a worse outcome reflects a more accurate measurement of renal function or an association with non-kidney factors such as inflammation [18-20].

**Inflammatory markers in acute coronary syndromes**

After the longest incubation period in human disease, a sudden and unheralded plaque rupture with the consequent occlusive or subocclusive coronary thrombus may happen randomly in the coronary tree independently from the plaque burden, changing a stable asymptomatic disease in an ACS. This is the final step of a longstanding process leading to weakening of the fibrous cap in which a number of inflammatory mechanisms are involved, including endothelial dysfunction, leukocyte migration, extracellular matrix degradation, and platelet activation [12]. In addition to biomarkers of myocardial necrosis used as diagnostic tools, cardiovascular-specific inflammation biomarkers are currently being used to identify subgroups of patients with ACS who are at increased risk for recurrent thrombotic cardiac events. Among the numerous inflammatory biomarkers addressing the separate aspects of ACS pathophysiology, CRP, an acute-phase protein produced by hepatocytes in response to inflammatory cytokines such as IL-6, has been frequently studied, gaining an independent short- and long-term clinical prognostic importance in the setting of ACS [21-25]. Although CRP concentrations may remain stable over long period of time, in patients with ACS they can rise markedly as happens in chronic inflammatory conditions. After the initial observations by Liuzzo et al [26], according to which levels of CRP >3 mg/L on admission predicted a dire in-hospital outcome, further studies underlined that discharge CRP values, and not admission values, were significantly related to short- and long-term outcome [22]. According to the evidence, recently the Study Group on Biomarkers in Cardiology of the Acute Cardiovascular Care Association of the European Society of Cardiology has pointed out that CRP measurement has neither value for diagnosis of ACS with or without ST-segment elevation nor for the choice of reperfusion therapy [27]. For secondary prevention after ACS and after PCI, a level of CRP ≥10 mg/L seems appropriate to identify high risk patients in whom an intensive risk factor modification can be useful [27]. While a treatment with high doses of statin has no effect on the variations of CRP values over the first month after the acute coronary episode [28], further significant decreases of CRP can be achieved over long stable phases of coronary disease with additional beneficial effects on prognosis [28,29]. About the significance of CRP elevations in ACS, the earliest observations on leukocytes inflammatory receptors gradient in coronary sinus but not in the post-obstructive chamber in patients with ACS together the highly significant positive temporal link between some inflammatory markers levels and release of troponin may be all considered a strong evidence favouring the hypothesis that inflammation is a response to even small amounts of myocardial necrosis [30-33]. Moreover, the lack of correlation between CRP increase in ACS and future recurrence of myocardial infarction makes very
unlikely that the former would be caused by the inflammatory process leading to plaque rupture and thrombus formation [33]. Furthermore, the development of a high-sensitivity assay (hsCRP) has permitted an accurate measurement of this biomarker in the apparently healthy population, where the fluctuations of CRP predictive of enhanced cardiovascular risk occur well below levels measured in acute illnesses [33]. The increase in the risk estimate of the higher quartile of hsCRP albeit modest is similar to the increment in risk prediction of total cholesterol and systolic blood pressure when added to age and sex [34]. Studies designed to test the hypothesis that a direct anti-inflammatory therapy reduces atherothrombotic coronary events are underway or in the planning stage [35].

Cystatin-C changes in acute coronary syndromes

A possible explanation for the predictive value of Cys-C for further cardiovascular events is that, independently from renal dysfunction, elevated serum concentrations of this marker would reflect a defensive response against the augmented secretion of lysosomal cathepsin associated to inflammatory processes related to the atherosclerotic disease. According to this hypothesis, the Cys-C levels should have a pattern similar to that already described for other inflammatory markers such as CRP and IL-6 during ACS, i.e. increase during acute phase and then return to baseline levels during the stable chronic phase. In a recent paper our group evaluated this still unexplored issue of the time course pattern of other established inflammatory markers (CRP, IL-6) and are not affected by myocardial necrosis. Moreover, our results indicate that Cys-C remains an accurate marker of renal function also during ACS because its levels do not change in case of left ventricular dysfunction, as detected by increased NT-proBNP values. The significant correlation between Cys-C and NT-proBNP observed at 6-week samples suggests that an established alteration in left ventricular function as result of the acute event may result in a derangement in renal function. The relatively low number of highly selected patients enrolled in the study and the paucity of the events at 1-year follow-up do not allow definite conclusions about the prognostic role of Cys-C in a population of all-comer patients with ACS.

Conclusions

In conclusion, our data seem to contradict the hypothesis that inflammation is a determinant of the Cys-C levels during ACS, because Cys-C levels do not show the time course pattern of other established inflammatory markers (CRP, IL-6) and are not affected by myocardial necrosis. Moreover, our results indicate that Cys-C remains an accurate marker of renal function also during ACS because its levels do not change in case of left ventricular dysfunction. The authors declare that they have no conflicting interests.

References


