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Role of Cystatin C in Coronary Artery Disease

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Abstract:

Over the past two decades, the increasing prevalence of CAD has become a serious public health burden and become one of the leading causes of death, disability, and rapidly rising costs in medical care. CHD has a complex etiopathogenesis and a multifactorial origin. In recent studies, it was shown that high level of cystatin c consider as a risk factor of Coronary Heart Disease.

Keywords: Cystatin C and Coronary Artery Disease, CAD.

Introduction:

A plausible link between increased cystatin C concentrations and impaired cardiovascular outcome, as reported in most of the studies so far, is renal dysfunction. However, none of the published studies so far has specifically addressed the issue of whether cystatin C is a predictor of cardiovascular risk even in patients with completely normal renal function (RF) **(1).**

An important common limitation of many of the studies mentioned in this review is that they have not measured GFR directly. Specific, well-designed trials are required to answer the important question of whether pathogenetic mechanisms other than renal dysfunction could account for a high cystatin C concentration and explain predictive value for future cardiovascular risk **(2).**

Inflammation, associated with atherogenic changes, may be one mechanism associated with cystatin C and cardiovascular risk, and high cystatin C concentrations have been found to be associated with high concentrations of CRP. Although it is possible that this association could just be the result of the presence of renal dysfunction, it has been suggested that high cystatin C concentrations are directly related to both inflammation and atherosclerosis **(3).**

There is evidence that both elastolytic cysteine proteases and their inhibitors, an important one being cystatin C, are involved in the pathogenesis of atherosclerosis. Studies have suggested that rather than the circulating levels, the imbalance between proteases and inhibitors determines their net effects on the cardiovascular system **(4).**

Inflammatory cytokines associated with atherosclerosis stimulate the production of lysosomal cathepsins, and increased plasma concentrations of cystatin C, a cathepsin inhibitor, may reflect, at least in part, an attempt to counterbalance a potentially damaging increased elastolytic activity **(5).**

Studies have demonstrated that human cathepsins are expressed in endothelial cells, smooth muscle cells, and macrophages, and that they are involved in the progression, the composition, and the rupture of atherosclerotic plaques. This response is likely to involve the interaction of mechanisms determined genetically **(6).**

High concentrations of cystatin C have also been associated with a hypermetabolic status. Given the various possible mechanisms responsible for changes in cystatin C concentrations, it is conceivable that, depending on the clinical setting considered, increased cystatin C concentrations may variously reflect renal dysfunction, the effects of heart failure on RF as a result of hypertension and/or fluid retention, or coronary artery disease associated with inflammation and atherosclerosis **(7).**

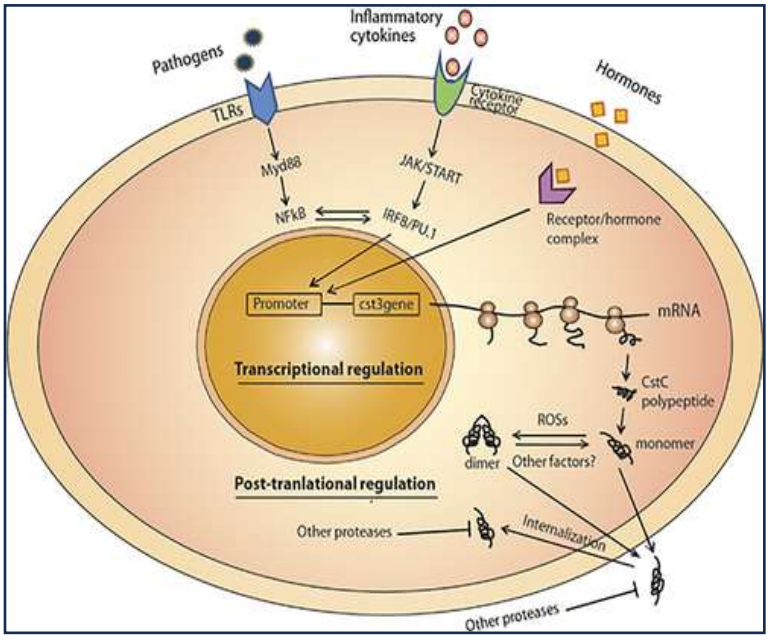

Figure (1): Cystatin C and inflammation. Multiple regulatory mechanisms exist to modulate the production and activity of cystatin C inside and outside of cells, at transcriptional and post-translational levels. JAK, Janus kinase; MyD88, myeloid differentiation primary response gene; ROSs, reactive oxygen species; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor **(8).**

Cystatin C levels and cardiovascular disease:

The participation has been reported of matrix metalloproteinases, serine, and lysosomal cysteine proteases in extensive extracellular matrix degradation and vascular wall remodeling. Atherosclerotic lesions in humans have shown an overexpression of elastolytic and collagenolytic cysteine proteases (cathepsins S, K, B, H, and L) and a decreased expression of cystatin C, their most abundant extracellular inhibitor **(1).**

There is also markedly increased expression of the various cathepsins within the AAA wall compared to healthy aorta. Moreover, weak overall expression of cystatin C was observed by immunohistochemistry in all the cells localized in the AAA with the exception of the luminal endothelial cells **(3).**

Many authors found reduced cystatin C in both atherosclerotic and aneurysmal aortic lesions, but normally expressed in vascular wall cells. Of note, decreased plasma cystatin C levels have been shown in patients with coronary artery ectasia coexisting with obstructive coronary artery disease (CAD), when compared to patients with obstructive CAD alone **(4).**

Furthermore, patients with AAA were shown to have lower cystatin C levels as compared to patients with obstructive abdominal aortic disease. In the past decade, many groups have assessed the effect of cystatin C on plaque formation **(2).**

Atherosclerotic mice (ApoE−/−/CysC−/−) deficient in cystatin C and apolipoprotein E displayed increased tunica media elastic lamina degradation, smooth muscle cells accumulation, and collagen content, but no difference in the size of aortic lesions induced by an atherogenic high-cholesterol diet **(6).**

Similarly, increased plaque size and macrophage content in the double knockout mice (ApoE−/−/CysC−/−) were reported when fed a high-fat diet. Evidence suggests that reactive oxygen species contribute to vascular oxidative stress, inflammation, and endothelial dysfunction, which have a very important role in atherogenesis and heart failure **(5).**

Interestingly, H2O2treatment causes elevation of cystatin C in the conditioned medium from cardiomyocytes. When cardiomyopathy was induced in mice by chronic administration of doxorubicin, elevated cystatin C protein was detected in the plasma and the myocardium **(4).**

Thus, cystatin C plays a role in cardiac extracellular matrix remodeling. Enhanced cysteine protease activity, due to the lack of cystatin C, favors inflammation in AAA lesions induced in atherosclerotic mice by promoting microvascularization and smooth muscle cell apoptosis as well as leukocyte adhesion and proliferation **(7).**

In addition, low cystatin C levels seem to reduce resistance to bacterial and viral infection, thus potentially enhancing chronic low-grade inflammatory stimuli responsible for aggressive plaque growth. Some investigators have also examined the influence of functional polymorphisms in cystatin C gene expression in order to elucidate the significance of cystatin C in pathological vascular remodeling in vivo **(9).**

Many authors found an association between a genetically determined decrease in cystatin C expression with increased severity of CAD. The mutant cystatin Chaplotype was associated with a greater number of coronary arteries stenoses, and serum cystatin C levels were lower in postinfarction patients than in controls **(1).**

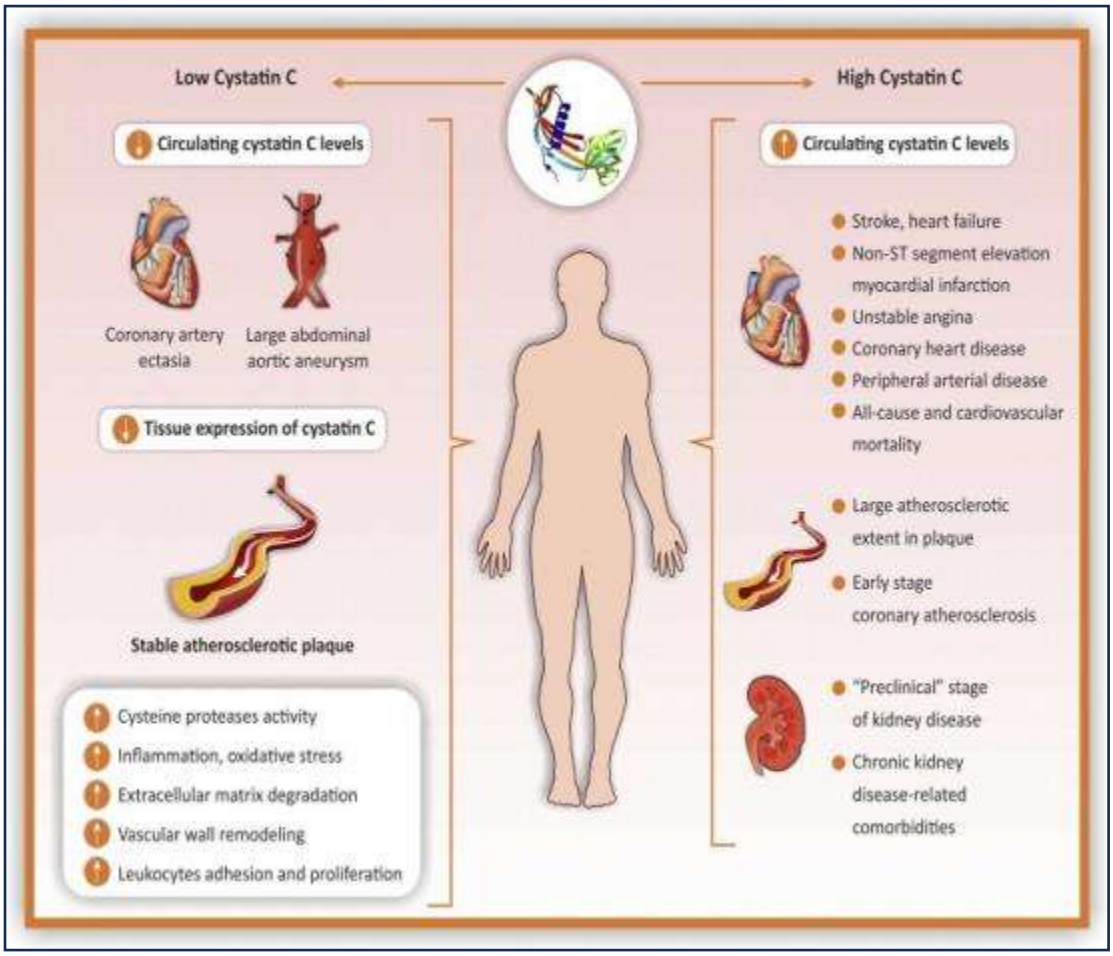

Figure (2): Controversial findings regarding the relationship between cystatin C and cardiovascular diseases **(10).**

Despite genetic variation in cystatin C gene expression, serum cystatin C values are found within the normal reference range in all subjects studied. Of interest, the cystatin C gene is of the housekeeping type, which indicates a stable production rate of cystatin C by most nucleated cell types **(3).**

Henceforth, several authors hypothesized that, unlike interleukin-6, C-reactive protein, and intercellular adhesion molecule-1, reduced baseline levels of cystatin C in healthy subjects might contribute to increased systemic atherosclerosis **(9).**

Contrary to these findings, a significant correlation was found between high serum cystatin C levels and cardiovascular risk factors in primary hypertensive patients. Likewise,

several epidemiological studies consistently report a positive and graded association between higher serum cystatin C levels and increased cardiovascular disease prevalence in individuals with GFR ≥60 ml/min/1.73 m^2 **(7).**

Cystatin C and CAD:

Cystatin is a lysosomal proteinase inhibitor and cysteine protease inhibitor. It is present in all tissues and body fluids. Recently its role in predicting onset and severity of cardiovascular disease is being studied. It is an established biomarker of kidney function **(1).**

Many studies have been done to evaluate the role of serum cystatin C in asymptomatic coronary artery disease with metabolic syndrome with normal renal function. The result of these studies showed that serum cystatin C has a significant association with CAD **(4).**

High plasma cystatin C levels are associated with severe CAD, proved angiographically, even in patients with normal renal function. Also, serum cystatin C can be used as a marker to predict the severity of atherosclerosis in suspected CAD patients **(6).**

Coronary ischemic events which are mainly due to rupture or fissuring of atherosclerotic lesions are thought to be the result of an imbalance between proteases which degrade extracellular matrix and protease inhibitors. Of the latter, cystatin C, a 13-kDa cysteine protease inhibitor, is believed to play a pivotal role in tissue remodeling because of its high concentration in biological fluids **(2).**

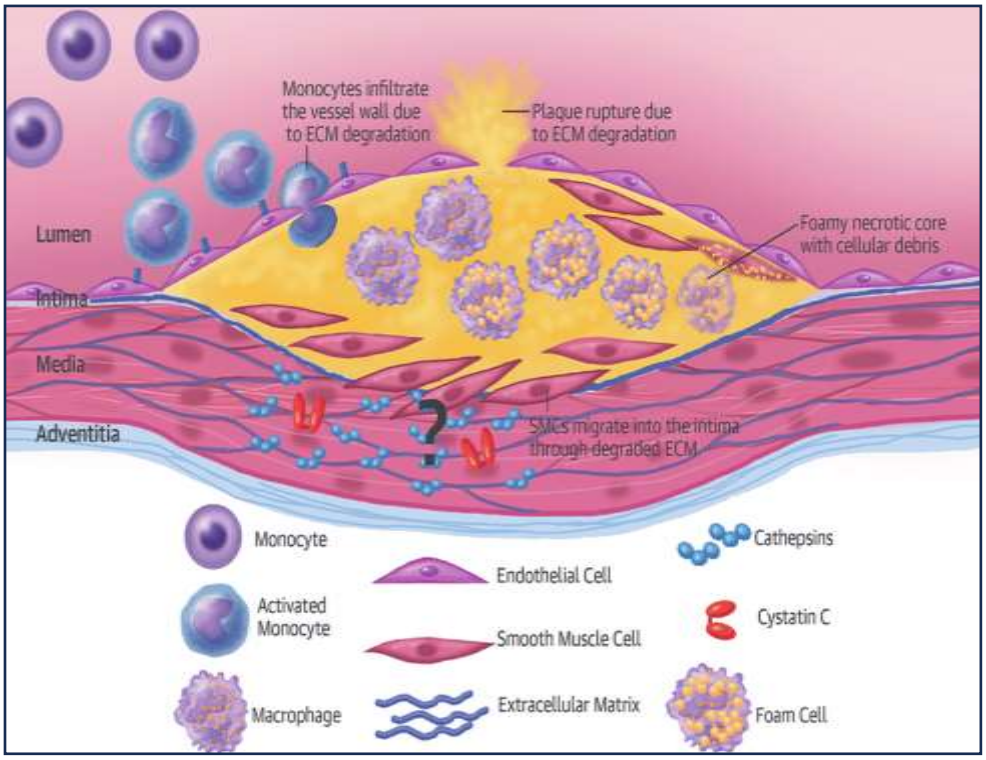

Figure (3): Presumed Mechanism of Cystatin C in Plaques **(11).**

Cystatin-C is normally expressed in vascular wall smooth muscle cells and inhibits elastase secreted by these cells. While cystatin C is present in normal arteries, immunostaining of cystatin-C has shown low expression in atherosclerotic plaques, suggesting that low levels of cystatin-C could be a risk factor for ischemic events **(5).**

Absolute or relative low levels of cystatin C in the artery wall injured by the inflammatory process of atherosclerosis would not counterbalance the increase in cysteine protease induced by pro-inflammatory cytokines **(1).**

Perspectives:

There are many possible explanations for the discrepancy between the tissue and circulating cystatin C levels. Considering the anti-atherogenic role of cystatin C, an imbalance between cysteine proteases and cystatin C would favor positive arterial remodeling **(9).**

On the other hand, the existence of a balance between cysteine proteases and their inhibitor cystatin C at the level of arteries and in circulation would offer protection against atherosclerosis and future cardiovascular events. Many studies indicated that statin therapy decreased proteolytic activity by reducing matrix metalloproteinase (MMP)-9, MMP-3, cathepsins H and L, and increasing cystatin C levels in the wall of AAAs **(3).**

Moreover, there is a consumption theory of circulating cystatin C in which low levels of this protein could be explained by its overuse against the surge in proteolytic activity. Another possible mechanism responsible for lower levels of serum cystatin C may be its chronic overuse through increased coronary atherosclerotic burden **(6).**

Subsequently, as a consequence of low cystatin C levels, an increased elastolytic activity of cathepsins would result in rapid degradation and progression of atherosclerotic plaques. In contrast, the relationship between elevated cystatin C level and cardiovascular damage may reflect an attempt to counterbalance a potentially damaging increased elastolytic activity **(4).**

Higher plasma cystatin C would result from cytokine-stimulated cells, which release cystatin C into circulation in the process of atherosclerosis and compensate for the decreased cystatin C in plaques. Other authors have also suggested that serum cystatin C levels might be increased during an inflammatory process in vulnerable plaque preceding and occurring along with the index cardiovascular or cerebrovascular event **(7).**

Thereafter, cystatin C levels would return to baseline levels with the recovery of the index event or calming down of plaque vulnerability. In the light of this information, it was assumed that cystatin C would have a dynamic physiology whose values may differ depending upon whether the CAD is acute or chronic **(9).**

For instance, high levels of cystatin C may raise the suspicion of non-ST-segment elevation acute coronary syndrome whereas lower cystatin C levels in a clinically stable patient would reflect a greater and stable atherosclerotic burden **(5).**

Nevertheless, there is also evidence that systemic pro-inflammatory factors, pro-thrombotic mediators, cytokines, and adipokines are intimately linked to the genesis of insulin resistance, metabolic syndrome, type 2 diabetes, atherosclerosis, and hypertension. These physiologic processes have been connected with end-organ damage, incident CKD, high cystatin C levels, and consequently higher cardiovascular risk and all-cause mortality **(2).**

Besides, CKD promotes hypertension, dyslipidemia, oxidative stress, and systemic inflammation, which in turn can contribute to the development of endothelial dysfunction and progression of atherosclerosis. Hence, cystatin C can detect a slight decrease in kidney function, which even within the normal range may promote arteriosclerosis **(4).**

Likewise, a very mild kidney dysfunction caused by atherosclerosis could be detected by cystatin C. It is also known that heart failure patients have a high prevalence of renal insufficiency with worse prognosis. This bidirectional heart–kidney interaction leads to a "vicious circle" and occurs at several levels through various pathways affecting hemodynamics, neurohumoral signaling, as well as salt and water homeostasis **(1).**

Although the normal physiology of the heart and kidney is well characterized, pathophysiological changes and mechanisms of organ dysfunction related to the cardiorenal syndrome are poorly understood. Taking all findings into consideration, many authors would propose different roles for cystatin C in the circulation and in the plaque **(2).**

Cystatin C might have limited and localized actions over cysteine proteases in vessel walls, which in its turn would not have influence over its systemic concentrations. Instead of compromising its use in clinical practice, the so called "non-GFR determinants" of cystatin C might concede to this marker the ability to recognize the effects of the systemic interactions on kidney function better than serum creatinine and even than direct measurements of GFR **(3).**

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