Original article

Cystatin C may not be a precious predictor for coronary artery disease and its severity: an area of uncertainty

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Summary. *Background and Aim:* Cystatin C, an endogenous indicator for kidney function, may be also an original indicator for coronary atherosclerosis. In the current study, we intended to assess its role in establishing the existence of coronary artery disease. We also attempted to present the best cut off point for Cystatin C to discriminate coronary disease from normal coronary condition. *Methods:* 147 consecutive patients who were candidate for coronary angiography were included into the study. Cystatin C was measured using Auto-analyzer system and by Gentian kit with enzyme calorimetric method. *Results:* The mean level of Cystatin C in the patients with and without coronary artery disease was 0.97±0.51 mg/l and 1.02±0.40 mg/l with no significant difference (p=0.564). In multivariate logistic regression model, the serum level of Cystatin C could not predict coronary artery disease (OR=1.199, 95% CI: 0.531 to 1.706, p=0.662). According to the area under the ROC curve, Cystatin C was not a good indicator to discriminate coronary artery disease from normal coronary condition (AUC=0.465, 95% CI: 0.372 to 0.559, p=0.470). Considering cut of points of 0.85 and 0.94 for Cystatin C, the sensitivity of this test for predicting coronary artery disease in comparison with coronary angiography was 65% and 51%, respectively. In assessing relationship between serum level of Cystatin C and other chemical biomarkers, Cystatin C was only correlated with serum triglyceride level (r=0.207, p=0.012). *Conclusions:* Cystatin C measurement may not be a suitable predictor for coronary artery disease and severity of the coronary involvement. Future studies with large sample size are necessitated to demarcate distinct role of Cystatin C in coronary artery disease. (www.actabiomedica.it)

Key words: Cystatin C, coronary artery disease, risk factors, biological markers

Introduction

Coronary artery disease (CAD) is one of the most important causes of morbidity and mortality around the world (1-3). Pathophysiological changes in CAD can be progressed by traditional coronary artery risk factors. Moreover, focusing on specific serum biomarkers as a risk profile has been more interested recently (4-6). Cystatin C, as one of such indicators, is a 13-kDa protein, which is a member of a family of competitive inhibitors of lysosomal cysteine protease produced in all nucleated cells at a normal rate that has been proposed as a choice marker for serum creatinine in evaluation of kidney function, predominantly to distinguish small drops in glomerular filtration rate (GFR) (7-9). Of interest, cystatin C has come out as an impending indicator for cardiovascular (CV) risk, as high levels of circulating cystatin C have been revealed to be constantly and robustly related with cardiovascular outcomes in diverse clinical scenarios (10-14). In addition, it has been recommended that elevated cystatin C levels are frankly related to both inflammation and atherosclerosis progression (15). Thus, cystatin C, as an endogenous pointer for renal function, can

be also a new marker for coronary atherosclerosis. In this study, we planned to assess the task of cystatin C in predicting the presence of coronary artery disease. We also attempted to present the best cut off point for Cystatin C to discriminate coronary disease from normal coronary condition.

Methods

In this study, 147 consecutive patients who were candidate for coronary angiography in Modarres hospital in 2014-2015 were included into the study. The study received ethical approval from the ethics committee of cardiovascular research center of Shahid Beheshti University of Medical Sciences. The selection method of patients for angiography was based on pre-procedural positive stress test. Those with eGFR <60 ml/min or serum creatinine >1.5 mg/dl, history of acute coronary syndrome within 3 months ago or undergoing coronary interventions, or having left ventricular dysfunction (LVEF <50%) were excluded from study. Coronary angiography was executed by standard Jud-kins technique. Coronary artery disease was described as coronary artery stenosis more than 50% in at least one coronary artery. In all subjects, the serum level of Cystatin C was measured using Auto-analyzer system (Hitachi912, Japan) and by Gentian kit (Germany) with enzyme calorimetric method. This study had two essential aims including determining relation between serum level of Cystatin C and severity of coronary artery disease and also establishing the best cut point to distinguish coronary artery disease from healthy condition. Results were showed as mean ± standard deviation (SD) for quantitative data and were reviewed by total frequencies and percentages for categorical data. Continuous variables were matched up using t test or non-parametric Mann-Whitney U test whenever the data did not emerge to have normal allocation or when the postulation of identical variances was conflicted across the groups. Categorical data were, on the other hand, matched up using chi-square test or Fisher's exact test when more than 20% of cells with estimated count of less than 5 were detected. The Pearson's correlation test was used to assess relations between the study measures. The measuring area un-

der the ROC curve was targeted for determining cut off point for Cystatin C. The statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was applied. P values less than 0.05 were considered statistically remarkable.

Results

The mean age of patients was 59.45±9.94 years, the mean body mass index was 27.54±4.51 and 49.7% were male. The mean serum creatinine level was 1.04±0.15 that were lower than 1.5 mg/dl in all subjects. Also, the mean eGFR was estimated 76.01±21.29. Regarding other biomarkers, the mean serum level of fasting blood sugar was 120.07±44.51 mg/dl, mean HbA1c was 7.11±1.66%, mean triglyceride level was 154.71±62.66 mg/dl, mean serum total cholesterol was 173.81±48.44 mg/dl, serum HDL level was 43.07±10.27 mg/dl, and serum LDL level was also 98.22±37.27 mg/dl. Mean LVEF was 55.75±7.59%. With regard to angiography results, 29.9% had normal coronary arteries, 21.8% had minimal CAD, 19.7% has single vessel disease, 16.3% had two-vessel disease, and 12.2% had three-vessel disease. Hence the coronary artery disease was established in 48.3% of participants.

The mean level of Cystatin C was 0.99±0.45 mg/l ranged 0.10 to 2.80 mg/l. Considering quartiles of Cystatin C as less than 0.7, 0.7 to 1.0, 1.0 to 1.3 and higher than 1.3 mg/l, the frequency of patients with each quartile was 20.4%, 27.9%, 25.2%, and 26.5%, respectively. The mean level of Cystatin C in those with and without coronary artery disease was 0.97±0.51 mg/l and 1.02±0.40 mg/l which showed no considerable difference (p=0.564). In multivariate logistic regression model, the serum level of Cystatin C could not predict coronary artery disease (OR= .199, 95% CI: 0.531 to 1.706, p=0.662). In this model, the key determinants of coronary artery disease included male gender (OR=6.3) and high level of fasting blood sugar (OR=1.10). According to the area under the ROC curve, Cystatin C was not a good indicator to discriminate coronary artery disease from normal coronary condition (AUC=0.465, 95%CI: 0.372 to 0.559, p=0.470) (Fig. 1). Considering cut of points of 0.85 and 0.94 for Cystatin C, the sensitivity of this test for predicting coronary artery
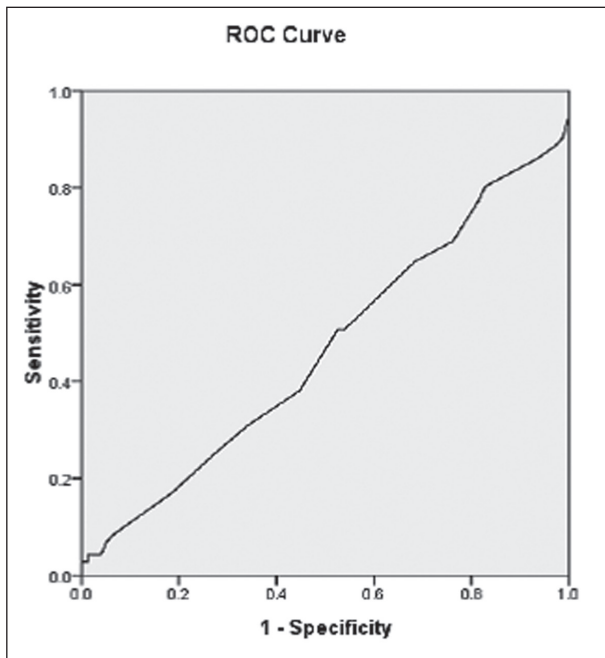
Figure 1. According to the area under the ROC curve, Cystatin C was not a good indicator to discriminate coronary artery disease from normal coronary condition (AUC=0.465, 95%CI: 0.372 to 0.559, p=0.470)

disease in comparison with coronary angiography was 65% and 51%, respectively. Also, no remarkable difference was showed in mean serum level of Cystatin C between normal coronary condition (1.04±0.45 mg/l), minimal CAD (0.98±0.31 mg/l), single vessel disease (1.06±0.58 mg/l), two-vessel disease (0.92±0.34 mg/l), and three-vessel disease (0.90±0.56 mg/l) (p=0.664) (Fig. 2). In assessing relationship between serum level of Cystatin C and other chemical biomarkers, Cystatin C was only correlated with serum triglyceride level (r=0.207, p=0.012) (Fig. 3).

Discussion

The current study was planned to weigh up the importance of measuring Cystatin C in predicting existence and severity of coronary artery disease. Also, to determine the role of this biomarker in metabolism different metabolic components including blood sugar and lipid profile, the association between this marker and these components was also assessed. Our study, however, could not demonstrate its role for predicting
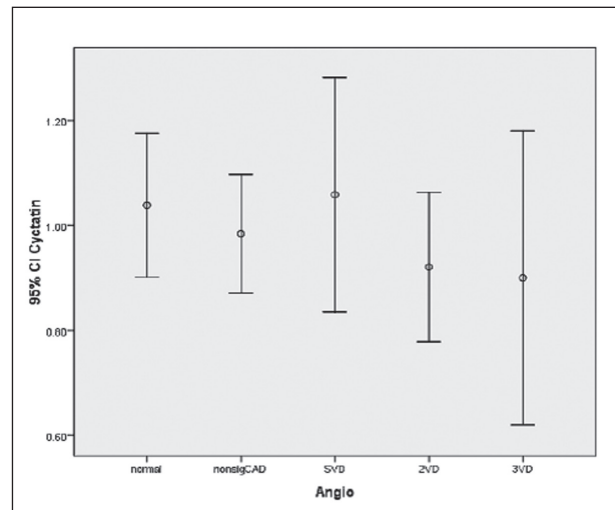

Figure 2. No significant difference was showed in mean serum level of Cystatin C between normal coronary condition (1.04±0.45 mg/l), minimal CAD (0.98±0.31 mg/l), single vessel disease (1.06±0.58 mg/l), two-vessel disease (0.92±0.34 mg/l), and three-vessel disease (0.90±0.56 mg/l) (p=0.664)
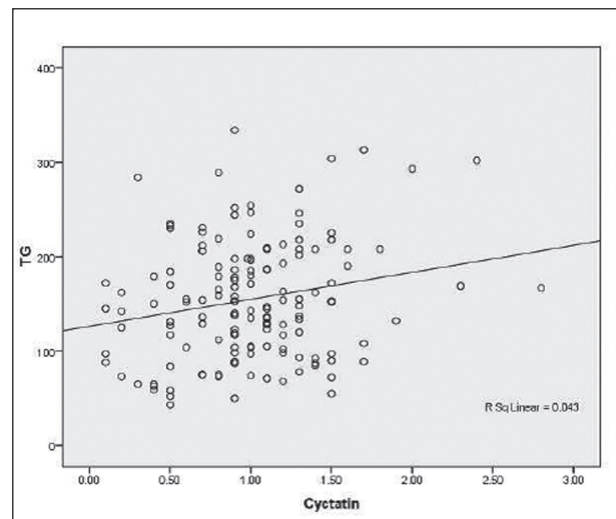

Figure 3. Cystatin C was only correlated with serum triglyceride level (r = 0.207, p = 0.012)

coronary artery disease and its severity. Also, among all other routine chemical profile, we could only show Cystatin C association with serum triglyceride. According to this fact that some studies could show high value of Cystatin C to predict presence and severity of coronary artery disease, our inconsequential results can be due to some reasons. First, because the present

study was focused on a sample of population, it can be concluded that Cystatin C may have no major pathophysiological role in progression of coronary atherosclerosis in this particular population. In fact, further studies should be focused the probable population-based gene polymorphisms involving Cystatin C formation and activation. Also, insignificant associations in our survey may be related to some technical problems in measuring Cystatin C. In addition, our findings might be affected by the cross-sectional feature of the study and small study sample size.

As previously pointed, some preceding studies could exhibit high value of Cystatin C in predicting coronary artery disease and its related adverse events. In a study by Doganer et al, Cystatin C levels were considerably lower in patients with CAD. It was notably lower in patients with significant CAD in comparison with those with nonsignificant CAD and normal cases. Serum levels of cystatin C along with the numbers of involved coronary vessels such as none, single-vessel, two-vessel, three-vessel, and four-vessel disease were in this fashion: 1334.86±393.45, 801.67±418.70, 993.90±457.34, 744.09±354.53, and 682.30±294.43, correspondingly (16). In another study by Koc et al, the number of patients with CAD enhanced as the quartile of cystatin C rose, and there was an outstanding difference between quartiles (p<0.001). Logistic regression analysis disclosed independent interpreters of incident CAD as Cystatin C, hs-CRP, eGFR, HDL cholesterol and SBP (p=0.005, p= 0.027, p=0.017, p=0.014 and p=0.001, respectively). Moreover, Cystatin C level was considerably associated with CAD severity score (b=0.258, p<0.01). A cut-off value of 0.82 mg/L for Cystatin C expected incident CAD with a sensitivity and specificity of 75.5% and 75.0% respectively (17). Cystatin C level also associated well with the atherosclerotic biochemical risk indicators like homocysteine, creatinine and hs-CRP. The robust association between chronic renal disorder and cardiovascular disease in conjunction with the rising understanding of the function of Cystatin C in the pathophysiology of CVD, motivated investigators to survey the potential association of Cystatin C with CVD. Throughout the continuum of CVD, unfavorable outcomes and risk stratification have been coupled with high plasma concentrations of Cystatin C (18). Although we did

not show association between level of Cystatin C and CAD, Cystatin C may be a helpful laboratory indicator in predicting the presence and severity of CAD in routine practice that should be more assessed in further studies.

Our study is considered as a pilot study and relatively small number of patients is undeniable limitation of our study. Our investigation could be as a new window for future large and multicenter studies which will illuminate more detailed results. Moreover, precious clinical and systematic reviews could be published from results of various centers. Cystatin C measurement may not be an appropriate predictor for coronary artery disease and its severity. Future studies with large sample size are needed to delineate distinct role of Cystatin C in coronary artery disease.

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