Cystatin C Associates with Metabolic Syndrome and Cardiovascular Events

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ABSTRACT

Introduction: Cystatin C is a serin protease inhibitor and secreted from all nucleated cells in the body. The present study was performed to evaluate the association of serum cystatin C level with metabolic syndrome and cardiovascular events in 5 years follow up period.

Method and materials: This study was consisted up 187 patients at the beginning of the study. After 5 years, 154 patients were re-evaluated and 33 were missed. Patients were divided into two groups according to the absence and presence of cardiovascular events as Group A and B. Initial metabolic and biochemical parameters were analyzed. Metabolic syndrome compounds were evaluated. Estimated glomerular filtration rate based on serum creatinine and cystatin C were calculated.

Results: Mean cystatin C level was 0.70 ± 0.18 mg/ml in group A and 0.98 ± 0.40 mg/ml in Group B, ($p<0.001$). Estimated glomerular filtration rate based on creatinine and cystatin C values were statistically significant decreased in group B, ($p<0.001$). Metabolic syndrome was determined 42.5% of Group A and 87.8% of Group B, ($p<0.001$). Multivariate logistic regression analysis pointed out that serum creatinine and cystatin C based on glomerular filtration rate are independent risk factors for cardiovascular events.

Conclusion: Initial serum cystatin C level and cystatin C based on glomerular filtration rate are independent risk factors for cardiovascular events.

Keywords: Cystatin C, Glomerular Filtration Rate, Metabolic Syndrome, Cardiovascular Event

INTRODUCTION

Molecular weight is 13 kDa, freely filtered by the renal glomerulus and catabolised in proximal tubules.[1,2] Plasma cystatin C concentration can be influenced by age, body mass index, gender, smoking and c-reactive protein.[3,4] Cystatin C is used for to measure glomerular filtration rate (GFR) and a reliable marker of renal functions.[5,6] Moreover, cystatin C is considered to be an alternative method to serum creatinine for estimating GFR.[7] Cystatin C correlates with chronic renal disease and complications. Therefore cystatin C can be a predictor of renal dysfunction and ischemic heart disease.[8] Acute coronary syndrome strongly associates with renal dysfunction as short and long-term outcomes.[9] Recent studies suggest that cystatin C is an independent risk factor for cardivascular events such as acute coronary syndrome, stroke and cardiovascular mortality.[10,11] The association of cystatin C with cardiovascular events may be attributed to inflammation and atherogenesis.[12] Cystatin C can be a useful marker to pedict cardiovascular events in long term. This study was performed to evaluate the importance of cystatin C on the cardiovascular events in 5 years follow up period.

METHOD AND MATERIALS

This study was consisted up 187 patients (112 female, 75 male) who admitted to Haseki Training and Research Hospital outpatient clinics in 2009 for routine controls. Initial metabolic and biochemical parameters, serum cystatin C levels and renal functions were measured. Patients with chronic renal, liver and heart diseases were exluded. Patients were evaluated after a 5 years period than divided into two groups as Group A (no cardiac events) and B (with cardiac events), than compared initial analyze values. Cardiovascular events were described as acute coronary syndrome, heart failure, stroke and mortality. 154 patients were re-evaluated and 33 were missed. Informed consent was taken from all patients. This study was approved by Haseki Training and Research Hospital's local ethic committee.

Blood pressure was measured twice with a mercury sphygmo-manometer from the right arm of patients in a sitting position after 5 minutes of rest. Waist circumference (WC) was measured between the lowest rib and the crista iliaca superior. Smoker patients were noted. Metabolic syndrome (MS) was diagnosed according to the National Cholesterol Education Program. Adult Treatment Panel (ATP) III criteria by presence of at least 3 of 5 criteria; [1] WC ≥94 cm for male, ≥80 cm for female; [2] arterial blood pressure ≥130/85 mmHg or presence of drug treatment for hypertension; [3] fasting blood glucose ≥100 mg/dl or drug treatment for hyperglycemia; [4] HDL Cholesterol <40 mg/dl in man. <50 mg/dl in women; [5] triglycerides ≥150 mg/dl or drug treatment for elevated triglyceride levels.

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Routine plasma biochemical parameters were analyzed with chemiluminescent method in Abbott Architect CI 16000 device (Illinois, USA). Serum cystatin C levels were measured with turbidimetric method in Roche Integra device (Mannheim, USA). Estimated glomerular filtration rate based on serum creatinine (eGFR-cre) was calculated by using MDRD (The Modification of Diet in Renal Disease) formula; 175 × (serum creatinine)1.154 × (age)0.203 × [0.742 (if female)].[13] eGFR based cystatin C (eGFR-cys) was calculated with 74.835 / [serum cystatin C] 1 / 0.75 formula.[14]

STATISTICAL ANALYSIS

Statistical analysis was carried out by using SPSS for Windows version 16.0. Results are expressed as mean ± standard deviation. Chi square test was used to evaluate categorical variables. A p value <0.05 was statistically significant. Logistic regression modeling was performed to identify relationship between cardiovascular events, cystatin C and eGFR values.

RESULTS

There were not seen any complication in 113 patients (Group A). Cardiovascular events recorded in 41 patients (Group B). Acute coronary syndrome, heart failure and stroke were developed in 37 and mortality in 4 patients. Basal metabolic and biochemical results of patients were presented in Table 1. Mean age was 42.11 ± 14.20 in Group A and 59.32 ± 11.87 in Group B, (p<0.001). Mean WC was 89.16 ± 14.39 cm in Group A and 100.90 ± 11.08 cm in Group B, (p<0.001). 75.6% were hypertensive of group B patients, (p<0.001). Fasting blood glucose (FBG) and HbA1c levels were 105.76 ± 54.75 mg/dl and 5.99 ± 1.60% in Group A and 126.61 ± 53.05 mg/dl and 6.96 ± 2.17% in Group B, (p:0.037 and 0.012). Mean urea and creatinine levels elevated in Group B. Also, HDL cholesterol and albumin levels decreased in Group B, (p:0.004 and 0.001). Mean cystatin C level was 0.70 ± 0.18 mg/ml in group A and 0.98 ± 0.40 mg/ml in Group B, (p<0.001). eGFR-cre and eGFR-cys values decreased statistically significant in group B, (p<0.001). Creatinine/cystatin C ratio was 1.30 ± 0.59 in Group A and 1.07 ± 0.26 in Group B, (p:0.02). Metabolic syndrome (MS) was determined 42.5% of Group A and 87.8% of Group B, (p<0.001). Multivariate logistic regression models were performed to demonstrate relationship between cardiovascular events and independent variables as age, MS, creatinine, cystatin C, eGFR-cre, eGFR-cys and creatinine/

Parameters	Group A (n: 113)	Group B (n: 41)	P value
Age	42.11 ± 14.20	59.32 ± 11.87	<0.001
Gender, male (%)	37.3 (%)	51.2 (%)	0.117
Smoker % (yes, n)	48.7% (n:55)	51.2% (n:21)	0.780
Waist circumference (cm)	89.16 ± 14.39	100.90 ± 11.08	<0.001
Hypertension (%)	35.4%	75.6%	<0.001
Glucose (mg/dl)	105.76 ± 54.75	126.61 ± 53.05	0.037
$HbA1_c$ (%)	5.99 ± 1.60	6.96 ± 2.17	0.012
AST (IU/L)	27.48 ± 41.35	39.10 ± 63.57	0.188
ALT (IU/L)	26.93 ± 35.46	28.22 ± 20.49	0.826
GGT (IU/L)	34.55 ± 58.17	46.95 ± 36.59	0.204
ALP (IU/L)	79.32 ± 41.13	88.88 ± 36.27	0.191
Albumin (g/dl)	4.34 ± 0.37	4.10 ± 0.46	0.004
Urea (mg/dl)	28.46 ± 13.04	37.73 ± 16.24	<0.001
Creatinine (mg/dl)	0.86 ± 0.24	0.99 ± 0.32	0.024
Total cholesterol (mg/dl)	189.46 ± 47.85	194.83 ± 39.09	0.525
Trigyceride (mg/dl)	164.05 ± 163.49	183.54 ± 129.31	0.492
HDL cholesterol (mg/dl)	42.08 ± 12.11	32.71 ± 8.02	<0.001
LDL cholesterol (mg/dl)	114.21 ± 37.15	122.59 ± 36.23	0.216
TSH (uIU/ml)	1.83 ± 1.30	1.59 ± 1.30	0.317
Uric acid (mg/dl)	4.59 ± 1.32	5.24 ± 1.02	0.120
CRP (mg/dl)	1.89 ± 3.18	2.15 ± 2.82	0.119
Sodium (mmol/L)	140.12 ± 2.13	140.51 ± 2.24	0.315
Potassium (mmol/L)	4.23 ± 0.42	4.22 ± 0.56	0.981
Calcium (mmol/L)	9.39 ± 0.47	9.23 ± 0.49	0.071
Cystatin C (mg/ml)	0.70 ± 0.18	0.98 ± 0.40	<0.001
eGFR-cre (ml/min/1.73 m^2)	96.09± 20.08	77.95 ± 22.08	<0.001
eGFR-cys (ml/min/1.73 m^2)	114.97 ± 21.08	86.44 ± 28.58	<0.001
cre/cys C ratio	1.30 ± 0.59	1.07 ± 0.26	0.020
Metabolic syndrome %	42.5%	87.8%	<0.001

(HbA1c: hemoglobin A1c, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ALP: alkaline phosphatase, TSH: thyroid stimulating hormone, CRP: c reactive protein, eGFR-cre: creatinine based estimated glomerular filtration rate, eGFR-cys: cystatin C based estimated glomerular filtration rate, cre/cys ratio:creatinine/cystatin C ratio)

Table-1: Comparison of metabolic and biochemical parameters of the study participants

Variables	P value	OR	95% CI
Model 1			
Age	0.006	1.055	1.016-1.096
MS	0.006	5.422	1.644-17.887
Cys C	0.021	10.343	1.413-75.716
Model 2			
Age	0.022	1.050	1.007-1.094
MS	0.007	4.801	1.526-15.100
eGFR-cys	0.033	0.977	0.957-0.998
Model 3			
Age	0.0001	1.075	1.035-1.116
MS	0.008	4.640	1.499-14.362
Creatinine	0.836	1.184	0.240-5.836
Model 4			
Age	0.001	1.086	1.033-1.036
MS	0.008	4.507	1.488-13.653
eGFR-cre	0.640	1.007	0.978-1.036
Model 5			
Age	0.0001	1.074	1.036-1.113
MS	0.01	4.405	1.429-13.584
cre/cys ratio	0.207	0.207	0.041-1.059

(MS: metabolic syndrome, eGFR-cre: creatinin based estimated glomerular filtration rate, eGFR-cys:cystatin C based estimated glomerular filtration rate, cre/cys ratio:creatinine/cystatin C ratio, OR: odds ratio, CI: confidence interval)

Table-2: Multivariate logistic regression models with serum cystatin C, serum creatinine, cystatin C and creatinin based estimated glomerular filtration rate and creatinine/cystatin C ratio with risk of cardiovascular events adjusted for age and metabolic syndrome

cystatin C ratio in Table 2. Age, MS, elevated cystatin C and decreased eGFR-cys were found to have an additional elevated risk for cardiovascular events.

DISCUSSION

Coronary artery disease and heart failure are outcomes of well established cardiac risk factors as hypertension, diabetes mellitus, metabolic syndrome and dyslipidemia. Cystatin C is considered to be a novel risk factor and prognostic cardiac parameter. Cystatin C has effects on transformation and presentation of antigens, neoplastic processes and inflammation.[15] Akerblom et al.[16] stated that cystatin C is associated with plaque rupture, vascular inflammation and myocardial necrosis. Serum cystatin C associates with ischemic heart and chronic kidney disease (CKD). Patients with cardiac events have a statistically higher serum urea, creatinine and cystatin C levels. Moreover age, MS, WC, hypertension, elevated FBG and HbA1c levels increased in patients with cardiovascular complications. These results were consistent with a decrease in eGFR-cre and eGFR-cys values. Renal dysfunction was observed with cardiovascular events.

Cushman et al.[17] stated that serum cystatin C is a better predictor than creatinine for the development of the preclinical renal dysfunction. Vigil et al.[18] reported that cystatin C is an independent predictor of cardiovascular events and total mortality in patients with chronic renal disease. In this study, initial elevated serum cystatin C level has a great importance for cardiovascular events (myocardial infarction, heart failure, stroke and mortality) for 5 years follow up period. Mortality was developed in 4 patients.

Cystatin C increases the risk of acute coronary syndrome and correlates strongly with left ventricular systolic injury.[19,20] Silva et al.[21] showed that cystatin C is an independent predictor of mortality in patients with stable angina and acute coronary syndrome. A logistic regression model analysis revealed that cystatin C and eGFR-cys are independent risk factors for cardiovascular events in our study. There was not a correlation between eGFR-cre and cardiovascular events.

Cystatin C and eGFR-cys predict cardiovascular prognosis in long term. Venetsanos et al.[22] pointed out that there is a significant correlation between cystatin C increase and troponin level in patients with acute myocardial infarction (AMI). Cystatin C has a prognostic value for patients with AMI.[23,24] Increased cystatin C level involves in the heart failure prognosis. Alehagen et al. revealed that cystatin C was correlated with pro-brain natriuretic peptide (p-BNP) and negatively correlated with left ventricular ejection fraction. Cystatin C increases with severity of heart failure as measured by NYHA functional class.[25] Plasma cystatin C and pro-BNP levels are independent predictors of mortality in patients with heart failure.[26,27] Serum levels of cystatin C were significantly higher in acute cerebral stroke patients with cerebral microbleeds.[28]

However creatinine/cystatin C ratio decreased in patients developed cardiovascular events which was consistent with an elevation in serum urea, creatinine and cystatin C, there was not a relationship between creatinine/cystatin C ratio and cardiovascular events according to the logistic regression analysis. On the other hand, creatinine/cystatin C ratio can be used to detect acute postrenal injury and significantly higher than that in subjects with intrinsic renal failure.[29-30]

CONCLUSION

In conclusion, basal serum cystatin C and eGFR-cys values were independent risk factors for cardiovascular events for 5 years in patients with no former chronic cardiac and renal disease. Cystatin C may predict cardiovascular prognosis in long term.

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