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Serum chromogranin A levels are associated with the SYNTAX score in coronary artery disease

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SUMMARY

OBJECTIVE: In this article, we investigated the association of chromogranin A with coronary artery disease.

METHODS: Biochemical parameters and chromogranin A levels obtained from peripheral blood samples during coronary angiography were analyzed in 90 patients. Patients were classified into two groups, namely, SYNergy between PCI with TAXUS and Cardiac Surgery score ≥1 (n=45) and SYNergy between PCI with TAXUS and Cardiac Surgery score=0 (n=45). This is a cross-sectional, prospective study.

RESULTS: Serum chromogranin A levels were significantly higher in the group with SYNergy between PCI with TAXUS and Cardiac Surgery score ≥1 compared to the group with SYNergy between PCI with TAXUS and Cardiac Surgery score=0 (1381.5±418.9 ng/mL and 1121.2±290.7 ng/mL, respectively; p=0.002). Serum chromogranin A levels were correlated with SYNergy between PCI with TAXUS and Cardiac Surgery score (r=0.556, p<0.04). ROC analysis showed that the area under the curve for serum chromogranin A levels was 0.687 (p=0.007), and the best cutoff value of 1,131 ng/mL had a sensitivity of 67% and a specificity of 65% for the prediction of coronary artery disease.

CONCLUSION: Serum chromogranin A levels were increased in coronary artery disease patients with SYNergy between PCI with TAXUS and Cardiac Surgery score ≥1. Increasing serum chromogranin A levels are proportional to the SYNergy between PCI with TAXUS and Cardiac Surgery score.

KEYWORDS: Chromogranin A. Coronary artery disease. Hypertension.

INTRODUCTION

Granins contain three types of proteins with acidic structure, namely, chromogranin A (CgA), chromogranin B, and secretogranin II. CgA is the major protein found in the nuclei of catecholamine storage vesicles of chromaffin cells and postganglionic sympathetic axons. CgA is stored and released together with catecholamines in chromaffin granules of neuroendocrine cells of the adrenal medulla[1,2]. It is an acidic protein of 439 amino acids with a molecular weight of 48 kDa. The prohormone CgA is metabolized by extracellular proteases (cathepsin, plasmin, and kallikrein) both in the cardiomyocyte cell membrane and in the extracellular matrix and cleaved into biologically active peptides[3,4]:

1. Catestatin (Cts),
2. pancreastatin, a dysglycemic peptide,
3. vasostatin-1, a vasodilator, antiadrenergic and antiangiogenic peptide,
4. serpinin, a proadrenergic peptide.

Plasma Cts concentration is a predictor of hypertension. Previous studies have observed elevated serum CgA levels and reduced Cts processing in hypertension. Cts levels have been shown to decrease, while plasma CgA level increases. Metabolic and vascular effects of CgA have been investigated and their role in hypertension and coronary artery disease has been studied. CgA levels have also been found to increase in heart failure, acute myocardial infarction, old age, pulmonary hypertension, and inflammatory diseases[5-8].

We investigated the relationship between serum CgA levels and SYNTAX scores in patients with coronary artery disease.

METHODS

Study population and study design

Patients who underwent coronary angiography from March 2020 to March 2021 for the diagnosis and treatment of coronary

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artery disease were included in the study. This is a cross-sectional, prospective study.

A SYNTAX score of all patients was calculated[9]. Patients were classified into two groups, namely, SYNTAX score=0 and SYNTAX score ≥1. Patients with more than 50% narrowing of the lumen diameter in at least one coronary artery were defined as the SYNTAX score ≥1 group. Patients with normal coronary arteries or non-significant coronary artery disease (less than 50% coronary stenosis) were defined as the SYNTAX score=0.

Baseline clinical and biochemical characteristics and blood pressure measurements were recorded during physical examination. The diagnoses of type 2 diabetes mellitus, hypertension, and hyperlipidemia were defined according to published guidelines. To avoid confounding effects, patients with acute coronary syndrome, a history of myocardial infarction and heart disease, heart failure, valvular heart disease, congenital heart disease, cardiomyopathy, stroke, chronic viral or bacterial infection, asthma, tumors, or immune system disorders were excluded. In addition, due to the possibility of elevated CgA levels, patients taking proton-pump inhibitors, H2 receptor antagonists, and somatostatin analogs, with renal failure, cirrhosis, chronic atrophic gastritis, irritable bowel disease, rheumatoid arthritis, hyperthyroidism, hyperparathyroidism, and breast, prostate, and colon cancers were also excluded from the study.

The study protocol was approved by the Ethics Committee of non-interventional clinical research and written informed consent was obtained from all subjects.

Qualitative evaluation of angiograms

All diagnostic coronary angiograms were scored according to the SYNTAX score (SYNergy between PCI with TAXUS™ and Cardiac Surgery) algorithm. The images were jointly reviewed by two cardiologists with more than 10 years of clinical experience. Coronary angiograms (visual assessment) were quantitatively evaluated for the presence of ≥50% stenosis in major epicardial coronary arteries and >1.5 mm branches. Patients who met the 50% diameter stenosis threshold by quantitative coronary angiographic information (QCA) were defined as SYNTAX score ≥1.

Biochemical analysis

Blood samples were collected from all participants after an overnight fast. Serum glucose, liver function, blood urea nitrogen, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured by standard laboratory techniques on a Cobas c8000 c502 Analyzer (Roche Diagnostics, Geneva, Switzerland). Serum levels of high-sensitivity C-reactive protein (hs-CRP) (Biocheck Laboratories, Toledo, OH, USA) were determined by ELISA.

Peripheral venous blood samples were collected from the antecubital vein after centrifugation at 3,000 rpm for 15 min. All serum samples were stored at -0°C until analysis. Serum CgA level was measured with a commercially available ELISA assay (human chromogranin-A catalog number E1730Hu). The standard curve range of the assay was 300–9,000 ng/L, and the intra-assay and inter-assay coefficients of variance were <8 and <10%, respectively. The sensitivity of the test is 15.21 ng/L.

Statistics

G * A total of 90 patients, 45 patients with SYNTAX score ≥1 and 45 patients with SYNTAX score=0, were included in the study by performing power analysis with an effect size of 0.5, a first-type error of 0.05, and a power of 0.95 using the Power 3.1 manual 2021 program. SPSS statistical package program was used for computerization and analysis of the data. Variables were expressed as mean (median), standard deviation (minumum-maximum), frequency, and percentage. The Shapiro-Wilk test was used to check whether the variables were normally distributed. The independent sample t-test (or Mann-Whitney U test) was used for measurement and independent two-group comparisons. A value of $p<0.05$ was considered statistically significant.

RESULTS

The baseline demographic, clinical, and biochemical characteristics of all participants are listed in Table 1. Compared with the SYNTAX score=0 group, patients in the SYNTAX score ≥1 group were older (51±7 years vs. 58±8 years; p=0.047) and had a higher number of male patients, [23(51%) vs. 29(64%); p=0.002] and a higher prevalence of smoking, [8 (17%) vs. 15(33%); p<0.001]; systolic blood pressure was higher (124±12 mmHg vs. 134±15 mmHg; p=0.042), type 2 diabetes was more frequent [16 (35%) vs. 22 (48%); p=0.001], and HDL cholesterol levels were lower (51±11 mg/dl vs. 36±15 mg/dL; p=0.034). Serum CgA levels were significantly higher in the SYNTAX score ≥1 group compared to the SYNTAX score=0 group (1381.5±418.9 ng/mL and 1121.2±290.7 ng/mL, respectively; p=0.002). There was a moderate to good significant and positive correlation between serum CgA levels and SYNTAX scores (r=0.556, p<0.04).

Multivariate logistic regression analysis

Multivariate logistic regression analysis was performed to determine the risk of more than 50% luminal stenosis of the

Table 1. Baseline clinical and biochemical characteristics of the study population.

Variable	SYNTAX score=0 n=45	SYNTAX score ≥1 n=45	p-value
Plasma CgA level, ng/mL	1121.2±290.7	1381.5±418.9	0.002
Age, years	51±7	58±8	0.047
Male, n (%)	23 (51)	29 (64)	0.002
Systolic blood pressure, mmHg	124±12	134±15	0.042
Diastolic blood pressure, mmHg	75±8	76±9	0.876
Type II diabetes mellitus, n (%)	16 (35)	22 (48)	0.001
Smoking, n (%)	8 (17)	15 (33)	<0.001
Hypertension, n (%)	25 (55)	32 (71)	<0.001
Hyperlipidemia, n (%)	18 (40)	19 (42)	0.828
Glucose, mg/dL	106±16	141±66	0.012
Creatinine, mg/dL	0.8±0.1	0.8±0.2	0.354
Urea, mg/dL	26±6	29±9	0.079
Total cholesterol, mg/dL	191±32	193±36	0.850
HDL cholesterol, mg/dL	51±11	36±15	0.034
LDL cholesterol, mg/dL	117±27	114±39	0.727
Triglycerides, mg/dL	162±75	194±90	0.284
CRP, mg/dL	1.6±1	3.2±1	0.101
Leukocytes, 10^6/mm^3	6.7±2.6	7.3±1.6	0.193
Neutrophils, 10^6/mm^3	3.7±1.2	4.6±1.4	0.009
Lymphocytes, 10^6/mm^3	2.0±0.5	2.1±0.6	0.403
Monocytes,10^6/mm^3	0.4±0.1	0.5±0.1	0.602
Hemoglobin, g/dL	14.2±1.6	13.7±1.5	0.246
Platelets, 10^3/mm^3	214±62	253±60	0.013

Data were expressed as number (%) and mean (SD). HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; CgA, chromagranin A.

coronary arteries as a function of traditional risk factors and biochemical variables (Table 2). Adjusted for traditional cardiovascular risk factor, male sex, age, smoking, hypertension, and hs-C-reactive protein were independent risk factors for coronary artery disease. When CgA was included in the multivariate regression analysis (Model 2), all remained significantly associated with a SYNTAX score ≥1 (Table 2). ROC analysis showed that the area under the curve for serum CgA levels was 0.687 (p=0.007), and the best cutoff value of 1131 ng/mL had a sensitivity of 67% and a specificity of 65% for the prediction of a SYNTAX score ≥1 (Figure 1).

Our study revealed that elevated serum CgA levels were moderately but significantly associated with the presence of coronary artery disease as determined by the SYNTAX score. These results, therefore, suggest a possible causal link between elevated CgA level and atherosclerosis. Cardiac CgA, in particular, is found to be stored in atrial granules together with natriuretic peptides involved in water and blood pressure regulation.

Plasma levels of natriuretic peptides have been observed to decrease in parallel with natriuretic peptides with treatment in patients with heart failure who were implanted with a left ventricular assist device. Corti et al. found that increased CgA levels were closely associated with mortality in patients with heart failure[10]. In patients with dilated and hypertrophic cardiomyopathy, circulating plasma CgA levels and B-type natriuretic peptide (BNP) levels were found to be high in correlation with each other. In another study of CgA, in heart failure, it has been shown to be a prognostic marker of the disease such as N-terminal proBNP[11]. In GISSI trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico), CgA was related to all-cause mortality or cardiovascular morbidity[12].

In GISSI trial, it was found that plasma CgA concentrations increased in proportion to disease severity[12].

Table 2. Multivariate stepwise logistic regression analysis for coronary artery disease risk.

Variable	OR (95%CI)	p-value
Model 1		
Age, years	1.9 (1.7–2.9)	<0.001
Gender, male	2.0 (1.5–2.7)	<0.001
Diagnosis of diabetes	1.3 (0.9–1.9)	0.082
Hyperlipidemia	1.4 (1.1–2.0)	0.071
Smoking	3.2 (2.3–6.5)	<0.001
hs-C-reactive protein	1.7 (1.2–2.5)	0.003
Model 2		
Age, years	2.0 (1.8–3.1)	<0.001
Gender, male	2.0 (1.4–2.7)	<0.001
Diagnosis of diabetes	1.1 (0.7–1.7)	0.212
Hyperlipidemia	1.2 (1.0–1.8)	0.121
Smoking	2.2 (1.3–4.5)	<0.001
hs-C-reactive protein	1.6 (1.1–2.3)	0.006
Plasma CgA level, ng/mL	1.6 (1.1–1.9)	0.036

OR indicates the odds ratio for significant coronary artery disease (CAD). CI, confidence interval.

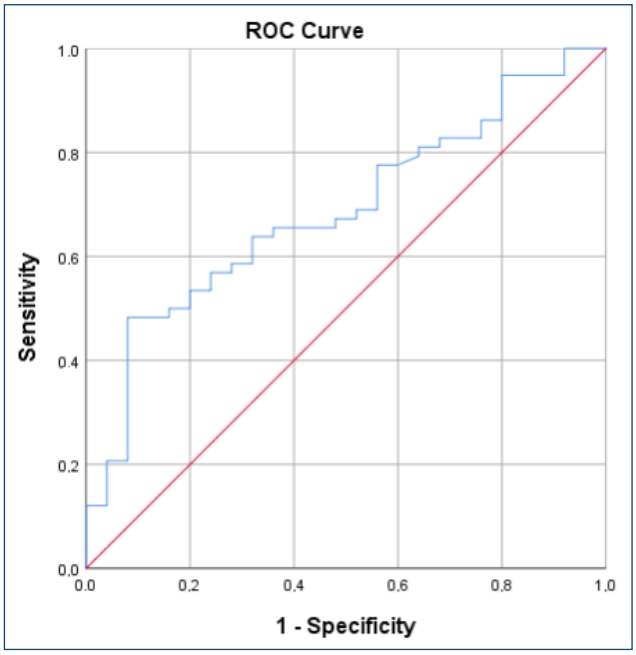

Figure 1. ROC curve testing the accuracy of serum CgA levels in predicting coronary artery disease (SYNTAX score ≥1). A optimal serum CgA cutoff value of 1,131 ng/mL provided the highest sensitivity (67%) and specificity (65%) for the prediction of coronary artery disease. The area under the curve for serum CgA levels was 0.687 (p=0.007). ROC: receiver operator characteristics; Syntax: SYNergy between PCI with TAXUS and Cardiac Surgery.

The effects of CgA at the vascular level are largely unknown. The 439 amino acid CgA (hCgA1-439) and its N-terminal fragments hCgA1-76 (vasostatin-1) and hCgA1-113 (vasostatin-2) have important roles in the regulation of the cardiovascular system[13]. These fragments can suppress vasoconstriction in isolated human conduit vessels. In another study, vasostatin-2 improved cardiac function and reduced remodeling, fibrosis, and inflammation in the heart in mice with myocardial infarction[14]. CgA and vasostatin-1 have been shown to have cardioprotective effects against Ischemia/reperfusion (I/R) injury.

Chromogranin A is physiologically degraded by tissue-specific proteases such as plasmin. Levels and activities of tissue plasminogen activator are reduced in inflammatory, diabetic vascular tissues and in smoking; therefore, this reduction may contribute to impaired CgA turnover. Vasostatin-1, produced by proteolytic cleavage of CgA, inhibits endothelin-1-induced vasoconstriction. This information is consistent with our idea that CgA is closely involved in the development of significant coronary artery disease. It also suggests that impaired processing of CgA occurs in the setting of atherosclerosis. In rodents, administration of Cts, a breakdown product of CgA, reduced hypertension, cardiac contractility, obesity, atherosclerosis and inflammation, and increased insulin sensitivity were observed. In contrast, pancreastatin, another breakdown product of CgA, has increased levels in diabetic patients. When given exogenously to rodents, obese mice have reduced insulin sensitivity and increased inflammation[15-18].

In the largest study on CgA levels in acute coronary syndromes, in which 1268 patients participated and followed up for 7.5 years, baseline CgA levels were associated with increased long-term mortality [OR 1.27 (95%CI 1.10–1.47)] and repeat myocardial infarction [OR 1.57 (95%CI 1.44–1.70), respectively[19]. In another study, a two-fold increase in plasma CgA levels was found 24 h after myocardial infarction.

Previous studies have suggested that the vascular protective activities of vasostatin-2, a CgA degradation product, are reduced in atherosclerosis or in the presence of diabetes due to low levels of proteolysis[20].

Another product produced by proteolytic cleavage of CgA is Cts. Although initially described as a physiological brake mechanism on catecholamine secretion, it reduces blood pressure, positively regulates baroreflex sensitivity and heart rate variability, and has cardioprotective effects. Cts induces nitric oxide synthesis from endothelial cells and cardiomyocytes. Based on *in vitro* and *in vivo* animal models, Cts has been shown to exhibit a potential cardioprotective effect by acting as a cardiodepressive peptide directly through multiple signaling pathways and may also reduce the apoptosis of

cardiomyocytes induced by oxidative stress. Chen et al. showed that serum Cts levels were lower in patients with stable angina pectoris (SAP) compared to healthy controls. Furthermore, a gradual decrease in serum Cts was found when stratifying CAD patients according to the number of diseased vessels. However, Liu et al. showed that SAP patients had significantly higher Cts levels compared to controls. The different findings are difficult to explain, Cts may increase as CgAs are released when pain occurs, and also the small patient sample size in Liu et al.'s study may have biased their results. Furthermore, Xu et al. showed that mean plasma Cts in patients with chronic total occlusion of the coronary arteries undergoing first-time coronary angiography or percutaneous coronary intervention was significantly higher than in patients with chest pain but normal coronary arteries[21-26].

In our study, elevated serum CgA level was an independent risk factor for coronary artery disease with severe luminal stenosis in multivariate regression analysis. Therefore, such data suggest the possible use of this molecule as a marker of atherosclerosis risk. Such studies will need to be validated using prospective cohort data.

This is a cross-sectional study, so while it allows for the identification of relationships, it does not allow for the inference of causality. Furthermore, several exclusion criteria and the selection of the study population may reduce the prognostic significance we found for CgA and introduce several selection biases. Large-scale, long-term prospective studies are needed to confirm our results and assess the prognostic significance of possible drugs that alter CgA levels.

The demonstration that elevated serum CgA levels are positively associated with the presence and severity of coronary artery disease provides a rationale for further research. More data are also needed to investigate the mechanisms underlying this relationship.

AUTHORS' CONTRIBUTIONS

AÇ: Conceptualization, Funding acquisition. **AD:** Data curation, Investigation, Project administration, Supervision, Writing – original draft. **MK:** Data curation. **SG:** Formal analysis, Visualization. **CA:** Methodology, Software. **MME:** Resources. **AY:** Validation. **AA:** Writing – review & editing.

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