



Association of Serum Cyclophilin A Levels with Severity of Coronary Artery Disease

Namilakonda Manaswini¹ Neelam N. Sreedevi² Sabitha Thummala² Kompella S.S. Saibaba²
Noorjahan Mohammed² Oruganti Sai Satish³

¹ Department of Biochemistry, ESIC Medical College and Hospital, Hyderabad, Telangana, India

² Department of Biochemistry, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

³ Department of Cardiology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Address for correspondence Namilakonda Manaswini, MD, Department of Biochemistry, ESIC Medical College and Hospital, Sanathnagar, Hyderabad, 500038, Telangana, India (e-mail: drkmanaswini@gmail.com).

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Abstract

Objective The disequilibrium between oxidant and antioxidant systems causes oxidative stress. Further, it disrupts the cell and releases reactive oxygen species (ROS), which in turn damages the vascular functions. Cyclophilin A (CypA), an immunophilin, is released in a highly regulated manner from vascular smooth muscle cells and multiplies the deleterious effects of ROS, associated with cardiovascular diseases. Thus, the aim of the present study is to correlate serum CypA levels with the severity of coronary artery disease (CAD).

Materials and Methods Study participants composed of 103 adult subjects, among whom 73 subjects were cases who were diagnosed as CAD angiographically. Thirty years of age and gender-matched subjects were taken as controls. The cases were further divided into single, double, and triple vessel disease subgroups. Blood samples were collected for the estimation of serum CypA, malondialdehyde (MDA), high-sensitive C-reactive protein (hsCRP), lipid profile, and plasma-glycated hemoglobin (HbA1C) by relevant biochemical methods.

Statistical Analysis The analysis was done using SPSS version 25. The data were expressed as median/mean and interquartile range/standard error. The groups were compared using the Mann–Whitney U-test and the Kruskal–Wallis test. *p*-Value less than 0.05 was considered statistically significant. Comparison of area under the curve (AUC) in receiver operating characteristic (ROC) curves was performed. A correlation was done by Spearman rank correlation.

Results The mean levels of serum CypA, hsCRP, and MDA in cases were significantly higher than those of controls (38 vs. 27 ng/mL, 18 vs. 5.1 mg/L, and 26 vs. 14 nmol/mL, $p < 0.001$). A positive correlation was observed between serum levels of CypA versus hsCRP and CypA versus MDA ($r = 0.36$ $p = 0.00$, $r = 0.52$, $p = 0.00$). At cut-off values greater than 33 ng/mL and 2.1 mg/L, serum CypA and hsCRP have 71% sensitivity, 93%

Keywords

- ▶ cyclophilin A
- ▶ hsCRP
- ▶ malondialdehyde
- ▶ coronary artery disease
- ▶ sensitivity
- ▶ biomarker

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specificity (AUC = 0.83), 84% sensitivity, and 70% specificity (AUC = 0.78) respectively. The number of occluded vessels was positively correlated with both CypA and hsCRP. Also, Serum CypA showed a significant positive correlation with HbA1C.

Conclusion Serum CypA can be used as a valuable biomarker for CAD.

Introduction

Coronary artery disease (CAD) is a main cause of death worldwide and has become a major public health concern in India.¹ The risk of CAD increases with conventional risk factors such as diabetes mellitus, hypertension, hyperlipidemia, obesity, and chronic kidney disease.² Apart from the traditional risk factors, oxidative stress is also a strong contender in the development of CAD.³ Oxidative stress hampers the activity of cells and releases reactive oxygen species (ROS). This in turn results in the secretion of cyclophilin A (CypA), a proinflammatory mediator from vascular smooth muscle cells (VSMCs) and macrophages.^{4–6} In earlier studies, it was demonstrated that the secretion of CypA is induced by excessive activation of Rho-kinase and oxidative stress specifically in VSMCs in a highly regulated manner.⁷

CypA is a member of the immunophilin family and has a peptidyl-prolyl isomerase activity which is involved in many biological functions like protein folding, cell signaling, and apoptosis-inducing factor.^{8,9} Moreover, extracellular CypA induces endothelial cell adhesion molecule expression, which promotes VSMC proliferation and migration. This plays a crucial role in promoting inflammation, vascular contraction, and the development of atherosclerosis.¹⁰ Further, CypA acts as a chemoattractant in conjunction with cytokines in inflammatory cells. Few earlier studies had found that CypA expression in mice is closely related to the development of intimal thickening and atherosclerosis.^{11–14}

Thus, CypA may have an important role in several stages of atherosclerosis as demonstrated by previous studies.^{12,15,16} However, very few studies were done on South Indian population. This study aimed to evaluate and correlate serum CypA levels and other biomarkers in cases and controls and to associate CypA levels with the severity of CAD.

Materials and Methods

This was a cross-sectional, comparative study of 73 patients and 30 controls, conducted in the Department of Biochemistry in collaboration with the Department of Cardiology, Nizams Institute of Medical Sciences (NIMS), Hyderabad. After approval from the Institutional Ethics Committee, patients aged between 35 and 75 years attending our hospital diagnosed as CAD angiographically were included as cases after obtaining informed consent. In this study, cases were further subdivided into three subgroups, according to the number of coronary vessels involved: single vessel (SVD), double vessel (DVD), and triple vessel diseased (TVD) patients. A narrowing of the lumen by more than 70% of the diameter was considered to indicate clinically significant

stenosis. Thirty years of age and gender-matched subjects were considered as controls. Patients with valvular and congenital heart disease, viral infections, asthma, Alzheimer's disease, rheumatoid arthritis, cancer, liver disease, kidney disease, stroke, and pregnancy were excluded.

Sample Collection and Testing

After 12 hour overnight fasting, 5 mL of fasting blood samples were taken. The serum was separated by centrifugation at 2,500 rpm for 20 minutes. High-sensitive C-reactive protein (hsCRP) and lipid profile (total cholesterol [TC], low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], very low-density lipoprotein-cholesterol, and triglycerides [TG]) were estimated immediately using a Beckman coulter AU 480 system. Malondialdehyde (MDA) was estimated by the thiobarbituric acid method. Glycated hemoglobin (HbA1c) was assayed on the D10 dual program based on chromatographic separation of the analytes by ion-exchange high-performance liquid chromatography. A part of the serum was aliquoted and stored at -20°C and serum CypA was analyzed by a double-sandwich enzyme-linked immunosorbent assay technique.

Statistical Analysis

The statistical analysis was done using SPSS software version 25. Normality for all the variables in controls and cases was checked by using the Shapiro–Wilk test. The data were expressed as mean \pm standard error/median (interquartile range) if the data were parametric/nonparametric, respectively. The two groups were compared using unpaired *t*-test and Mann–Whitney U-test for normal data and nonnormal data, respectively. *p*-Value less than 0.05 was considered statistically significant. One-way ANOVA (analysis of variance)/Kruskal–Wallis (parametric/nonparametric) test was performed to compare the means between more than two groups. Comparison of area under the curve (AUC) in receiver operating characteristic (ROC) curves was performed. Spearman rank/Pearson correlation was measured for nonparametric/parametric data. Logistic regression was done to assess the contribution of each parameter to the development of CAD.

Results

About 103 participants (range: 35–75 years, 75% males and 25% females) were enrolled in the present study. Baseline characteristics are shown in ►Table 1. There are a higher number of males (84%), smokers (56%), and alcoholics (60%) in the TVD group when compared with that in SVD and DVD

Table 1 Baseline characteristics of cases group

	Variable	SVD group (N = 24)	DVD group (N = 24)	TVD group (N = 25)
Sex (%)	Males	19 (79%)	17 (70%)	21 (84%)
	Females	5 (21%)	7 (30%)	4 (16%)
Diabetes (%)	Nondiabetics	12 (50%)	8 (33%)	14 (56%)
	Diabetics	12 (50%)	16 (67%)	11 (44%)
Hypertension (%)	Nonhypertensives	8 (33%)	10 (41%)	10 (40%)
	Hypertensives	16 (67%)	14 (59%)	15 (60%)
Smoker (%)	Nonsmokers	13 (54%)	11 (46%)	14 (44%)
	Smokers	11 (46%)	13 (54%)	14 (56%)
Alcoholic (%)	Nonalcoholics	13 (54%)	13 (54%)	10 (40%)
	Alcoholics	11 (46%)	11 (46%)	15 (60%)

Abbreviations: DVD, double vessel disease; SVD, single vessel disease; TVD, triple vessel disease.

groups as shown in ► **Table 1**. In DVD groups there are higher numbers of diabetics (67%).

Demographic and biochemical variables of cases and controls are shown in ► **Table 2**. The median age group in controls is 53 years while that in cases is 55 years. There was no significant difference between the age groups ($p = 0.82$) (► **Table 2**). Serum CypA level was significantly higher in cases when compared with controls with a mean 38 ng/mL and 27 ng/mL respectively (p -value < 0.001). Also, we found significantly higher values of serum MDA, serum hsCRP, and HbA1C in cases than controls (► **Table 2**).

As shown in ► **Table 3**, in the present study we found a statistically significant increase in serum CypA levels in DVD and TVD when compared with the control group. However,

we could not find any significant difference between controls and SVD. Also, we found significantly higher levels of serum CypA in DVD and TVD when compared with SVD cases. However, we did not find any significant difference between DVD and TVD patients.

In this study, we found significantly higher levels of serum hsCRP in DVD and TVD when compared with controls. We also found significantly higher levels of serum MDA ($p < 0.001$) and HbA1c ($p < 0.001$) in SVD, DVD, and TVD patients when compared with controls.

As shown in ► **Table 4**, we could not find any statistically significant difference between serum CypA levels with CAD with diabetes mellitus and CAD without diabetes ($p = 1.00$). In ► **Table 5**, a significant positive correlation was found between serum CypA and both hsCRP and MDA ($r = 0.36$,

Table 2 Demographic and biochemical variables of cases and controls

Variable	Controls (N = 30) Median (IQR) or mean \pm SE	Cases (N = 73) Median (IQR) or Mean \pm SE	p-Value (< 0.05)
Age (y)	53 (52–59)	55 (50–62)	0.82
Gender (M:F)	3:1	3:1	–
TC (mg/dL)	163 \pm 7.9	152 \pm 6.5	0.78
HDL-C (mg/dL)	38 \pm 2.1	32 \pm 1.0	$< 0.001^a$
LDL-C (mg/dL)	61 \pm 8.6	88 \pm 4.9	0.003 ^a
TG (mg/dL)	138 \pm 15	161 \pm 18	0.077
AIP (log TG/HDL)	4.2 \pm 0.6	5.1 \pm 0.5	0.002 ^a
HbA1C (%)	5.1 \pm 1.5	7.1 \pm 0.3	$< 0.001^a$
S.MDA (nmol/mL)	14 \pm 1.9	26 \pm 1.5	$< 0.001^a$
hsCRP (mg/L)	5.1 \pm 1.5	18 \pm 3.1	$< 0.001^a$
CypA (ng/mL)	27 \pm 1.0	38 \pm 1.6	$< 0.001^a$

Abbreviations: AIP, atherogenic index of plasma; CypA, cyclophilin A; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitive C-reactive protein; IQR, Interquartile range; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; SE, standard error; TC, total cholesterol; TG, triglyceride.

Note: Data presented as median (IQR) or mean \pm SE.

^aStatistically significant values ($p < 0.05$).

Table 3 Demographic and biochemical variables of SVD, DVD, TVD, and Control groups

Variable	Controls (N = 30)	SVD (N = 24) Median (IQR) or mean ± SE	DVD (N = 24) Median (IQR) or mean ± SE	TVD (N = 25) Median (IQR) or mean ± SE	p-Value
Age (y)	53 (43–70)	52.5 (46–59)	55 (47–61)	58 (54–67)	0.07
TC (mg/dL)	163 ± 7.9	156 ± 8.4	152 ± 7	143 ± 6.3	0.233
HDL (mg/dL)	38 ± 2.1	32 ± 1.2	32 ± 1.1	30 ± 1.6	0.004 ^a
LDL (mg/dL)	61 ± 8.6	82 ± 7.3	89 ± 4.7	85 ± 5.1	0.018 ^a
TG (mg/dL)	138 ± 15	206 ± 26	155 ± 21	153 ± 9.4	0.04 ^a
AIP (log TG/HDL)	4.2 ± 0.6	6.4 ± 0.6	4.9 ± 0.6	5.4 ± 0.4	0.004 ^a
HbA1C (%)	5.1 ± 1.5	6.4 ± 0.2	7 ± 0.3	7.4 ± 0.4	< 0.001 ^a
MDA (nmol/mL)	14 ± 1.9	26 ± 1.0	27 ± 5.4	39 ± 2.6	0.001 ^a
hsCRP (mg/L)	5.1 ± 1.5	11 ± 2.2	17 ± 3.6	30 ± 6.4	< 0.001 ^a
CypA (ng/mL)	27 ± 1.0	30.4 ± 1.7	39 ± 1.8	50 ± 2.9	< 0.001 ^a

Abbreviations: AIP, atherogenic index of plasma; CypA, cyclophilin A; DVD, double vessel cases; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein; IQR, Interquartile range; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; SE, standard error; SVD, single vessel disease; TC, total cholesterol; TG, triglyceride; TVD, triple vessel disease.

Note: Data are presented as median (IQR) or mean ± SE.

^aStatistically significant values ($p < 0.05$).

Table 4 Comparison of serum CypA levels with CAD without DM and CAD with DM

	CypA (ng/mL)	p-Value
Control	27	< 0.001 (vs. CAD – DM) ^a < 0.001 (vs. CAD + DM) ^b
CAD – DM	38.7	1.00 ^c
CAD + DM	40.6	

Abbreviations: CAD, coronary artery disease; CypA, cyclophilin A; DM, diabetes mellitus.

^aControl vs. (CAD – DM) CAD without DM.

^bControl vs. (CAD + DM) CAD with DM.

^cCAD without DM vs. CAD with DM.

Table 5 Correlation of Serum Cyclophilin A with other variables in the CAD group

Variable	r	p-Value
MDA (nmol/mL)	0.52	< 0.001 ^a
hsCRP (mg/L)	0.36	< 0.001 ^a
HbA1C (%)	0.36	< 0.001 ^a
TC (mg/dL)	–0.2	0.02 ^a
HDL (mg/dL)	–0.1	0.17
LDL (mg/dL)	0.2	0.03 ^a
TG (mg/dL)	–0.5	0.69

Abbreviations: HDL, high-density lipoprotein; hsCRP, high sensitive C-reactive protein; LDL, low-density lipoprotein; MDA, malondialdehyde; TC, total cholesterol; TG, triglyceride.

^a $p < 0.05$ is considered statistically significant.

$p < 0.001$; $r = 0.52$, $p < 0.001$). Also, there was a significant positive correlation with HbA1C ($r = 0.36$, $p < 0.001$). A significant positive correlation was found between the number of occluded vessels and both CypA levels and hsCRP, with

Table 6 Correlation between number of occluded vessels and cyclophilin A and hsCRP

Spearman correlation	r	p
CypA (ng/mL)	0.73	< 0.001 ^a
hsCRP (mg/L)	0.67	< 0.001 ^a

Abbreviations: CypA, cyclophilin A; hsCRP, high sensitive C-reactive protein.

^a $p < 0.05$ is considered statistically significant.

Table 7 Diagnostic performance of serum CypA and hsCRP

Variable	CypA	hsCRP
Cut-off	> 33 (ng/mL)	> 2.1 (mg/L)
AUC	0.83	0.78
Sensitivity (%)	71	84
Specificity (%)	93	70

Abbreviation: AUC, area under the curve; CypA, cyclophilin A; hsCRP, high sensitive C-reactive protein.

$r = 0.73$, $p < 0.001$, and $r = 0.67$, $p < 0.001$ respectively, among all groups (►Table 6).

The ROC curve analysis demonstrated that the level of CypA is better than hsCRP in predicting CAD (►Table 7). At a cut-off of greater than 33 ng/mL, CypA has 71% sensitivity and 93% specificity in diagnosing CAD with an AUC of 0.83. Serum hsCRP has 84% sensitivity and 70% specificity at a cut-off value greater than 2.1 with an AUC of 0.78 (►Table 7, ►Fig. 1).

Logistic regression was used to estimate the association between serum CypA levels and CAD. In the present study,

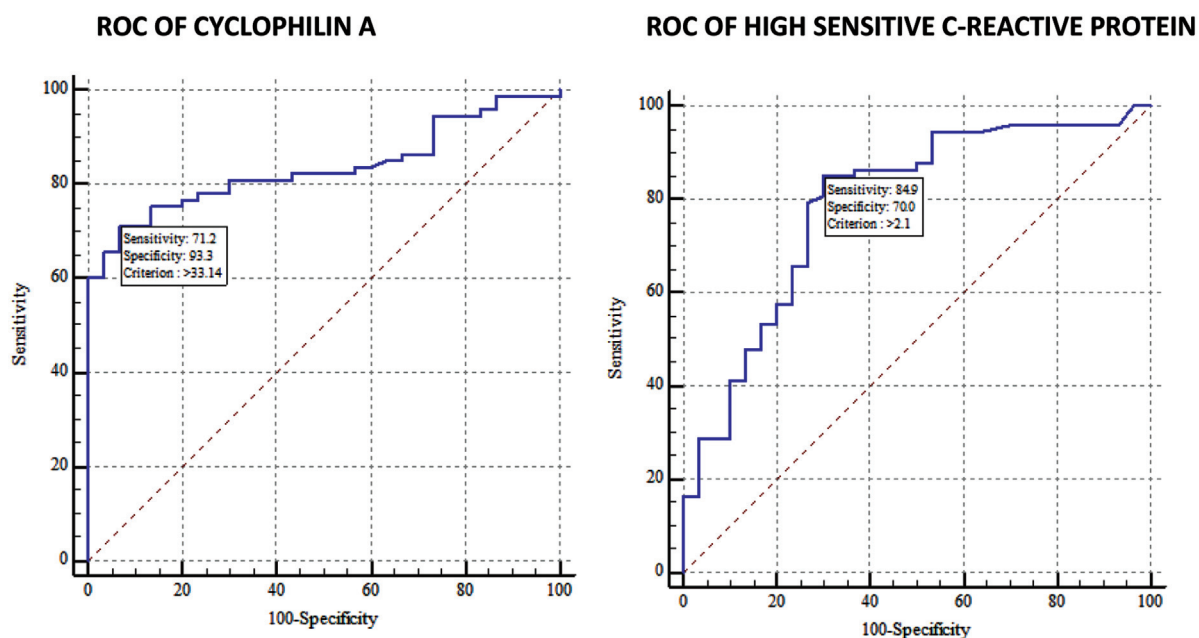


Fig. 1 ROC curve for CypA and hsCRP. CypA, cyclophilin A; hsCRP, high sensitive C-reactive protein; ROC, receiver operating characteristic.

Table 8 Logistic regression analysis

Variable	Coefficient	Std. error	<i>p</i>
Age (y)	-0.002	0.05	0.96
CypA (ng/mL)	0.1	0.06	0.025^a
hsCRP (mg/L)	0.06	0.04	0.18
MDA (nmol/mL)	0.187	0.06	0.005^a
TC (mg/dL)	-0.05	0.02	0.04^a
TG (mg/dL)	0.02	0.007	0.008^a
HDL (mg/dL)	-0.13	0.06	0.042^a

Abbreviations: CypA, cyclophilin A; HDL, high-density lipoprotein; hsCRP, high sensitive C-reactive protein; MDA, malondialdehyde; TC, total cholesterol; TG, triglyceride.

^a*p* < 0.05 is taken statistically significant.

CypA, MDA, and TG were found to be positive predictors and HDL was found to be a negative predictor for CAD (► **Table 8**). TC in the present study was found to be a negative predictor, which may be due to the use of statins in the cases group as the cases were taken from a tertiary care center.

Discussion

CypA plays an important role in protein folding, trafficking, and regulates the immune system.¹¹ Besides, it seems to play a crucial role in cardiovascular diseases (CVD). In the present study, we estimated serum levels of CypA and two oxidative/inflammatory markers in cases in comparison to controls, to know their relationship and to know if the serum CypA has a role in CVD. Serum levels of CypA were statistically significantly higher in patients proven with angiographically verified coronary atherosclerosis (mean = 38 ng/mL) than

control (mean = 27 ng/mL), with a *p*-value of less than 0.001 in the current study. This is in line with other studies that showed that serum CypA levels were higher among the patient group than the control group.^{17–20} Yan et al also found that serum concentration of CypA in patients with the acute coronary syndrome was significantly higher than those with stable angina and controls.²¹ Moreover, we also found a statistically significant increase in the mean CypA concentration in DVD and TVD patient groups in comparison with the control group (*p* < 0.001). Although the mean CypA levels of SVD cases were higher when compared with controls, we could not find any significant difference. Serum CypA levels increased sequentially within the coronary stenosis group as the number of stenotic vessels increased (*p* < 0.001). This explains a possible role of CypA in atherosclerosis. As the severity of the disease is increased, there is increased generation of ROS due to oxidative stress. For this reason, CypA is secreted in a highly regulated manner in response to ROS from endothelial cells.²² Moreover, it helps us to know the progression of the disease as the mean serum CypA is higher in TVD when compared with DVD and SVD. This is similar to a study, Satoh et al, who proved that CypA was elevated in patients with SVD, DVD, or TVD (all showing *p* < 0.001) compared with the control group (no organic stenosis/no vasospastic angina).⁵

In the present study, we observed elevated plasma levels of CypA and CAD in patients with and without type 2 diabetes, which is on par with the study done by Vinitha et al.²³ The CAD + DM (CAD with diabetes mellitus) group did not differ significantly from the CAD – DM (CAD without diabetes) concerning the CypA levels (*p* = 1.00). This is in contrast with the study done by Yossef et al.²⁴

We also found a significant increase in levels of serum MDA in cases when compared with controls, which is similar

to other studies.^{25–28} The increased lipid peroxidation (MDA) occurs as a consequence of oxidative stress when the balance between oxidant and antioxidant status is impaired.²⁹ The study results also indicated a significantly increased serum MDA, as a potent marker of lipid peroxidation in CAD patients compared with control groups, which correlated with disease severity.

According to the study, we found a significant increase in hsCRP levels in cases when compared with controls, which is similar to other studies.^{30,31} We found no significant increase in hsCRP levels in SVD, DVD, and TVD cases. But when compared with controls there was a significant increase in levels with SVD, DVD, and TVD separately.^{30,31} This increase in CRP concentrations might be associated with the fact that CRP binds to the LDL particle in atherosclerotic plaques leading to activation of complement, thus, being proinflammatory and contributing to atherogenesis. A study by Satoh et al⁵ had suggested the use of CypA in conjunction with CRP as a predictor of risk in CAD. Additionally, we also found that levels of CypA were correlated positively with hsCRP, MDA, LDL-C, and HbA1C, which is in line with other studies.^{24,32}

In the current study, CypA, MDA, and TG were found to be positive predictors and HDL was found to be a negative predictor for CAD. Moreover, ROC analysis in this study showed that CypA (AUC = 0.83) is a better predictor than hsCRP (AUC = 0.78). These findings indicate the potential use of plasma CypA level as a marker of proinflammatory status.

Conclusion

This study demonstrates that serum CypA helps predict the severity of disease and in knowing the progression of CAD. Other studies have also established serum CypA as a good marker for CAD. Further studies with a large number of cases will help to establish the clinical significance of CypA in the pathogenesis of atherosclerotic CVD and also to know its usefulness as a biomarker for CAD.

Ethical Clearance

The study was approved by the hospital's institutional ethical committee (EC/NIMS/1673/2015).

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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