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

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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%
Introduction
Coronary artery disease (CAD) is a main cause of death worldwide and has become a major public health concern in India. The risk of CAD increases with conventional risk factors such as diabetes mellitus, hypertension, hyperlipidemia, obesity, and chronic kidney disease. Apart from the traditional risk factors, oxidative stress is also a strong contender in the development of CAD. 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. 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.

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. 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. 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.

Thus, CypA may have an important role in several stages of atherosclerosis as demonstrated by previous studies. 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.

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 ± 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
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, p < 0.05).

### 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.

### Table 2 Demographic and biochemical variables of cases and controls

| Variable       | Controls (N = 30) | Cases (N = 73) | 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 ± 7.9         | 152 ± 6.5     | 0.78            |
| HDL-C (mg/dL)  | 38 ± 2.1          | 32 ± 1.0      | < 0.001*        |
| LDL-C (mg/dL)  | 61 ± 8.6          | 88 ± 4.9      | 0.003*          |
| TG (mg/dL)     | 138 ± 15          | 161 ± 18      | 0.077           |
| AIP (log TG/HDL)| 4.2 ± 0.6        | 5.1 ± 0.5     | 0.002*          |
| HbA1C (%)      | 5.1 ± 1.5         | 7.1 ± 0.3     | < 0.001*        |
| S.MDA (nmol/mL)| 14 ± 1.9          | 26 ± 1.5      | < 0.001*        |
| hsCRP (mg/L)   | 5.1 ± 1.5         | 18 ± 3.1      | < 0.001*        |
| CypA (ng/mL)   | 27 ± 1.0          | 38 ± 1.6      | < 0.001*        |

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 ± SE.

*Statistically 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   |
| LDL (mg/dL)       | 61 ± 8.6          | 82 ± 7.3                               | 89 ± 4.7                               | 85 ± 5.1                               | 0.018   |
| TG (mg/dL)        | 138 ± 15          | 206 ± 26                               | 155 ± 21                               | 153 ± 9.4                              | 0.043   |
| AIP (log TG/HDL)  | 4.2 ± 0.6         | 6.4 ± 0.6                              | 4.9 ± 0.6                              | 5.4 ± 0.4                              | 0.004   |
| HbA1C (%)         | 5.1 ± 1.5         | 6.4 ± 0.2                              | 7 ± 0.3                                | 7.4 ± 0.4                              | < 0.001 |
| MDA (nmol/mL)     | 14 ± 1.9          | 26 ± 1.0                               | 27 ± 5.4                               | 39 ± 2.6                               | 0.001   |
| hsCRP (mg/L)      | 5.1 ± 1.5         | 11 ± 2.2                               | 17 ± 3.6                               | 30 ± 6.4                               | < 0.001 |
| CypA (ng/mL)      | 27 ± 1.0          | 30.4 ± 1.7                             | 39 ± 1.8                               | 50 ± 2.9                               | < 0.001 |

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.

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

|         | CypA (ng/mL) | p-Value |
|---------|--------------|---------|
| Control | 27           | < 0.001 |
| CAD – DM| 38.7         | < 0.001 |
| CAD + DM| 40.6         | < 0.001 |

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

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 |
| hsCRP (mg/L)    | 0.36  | < 0.001 |
| HbA1C (%)       | 0.36  | < 0.001 |
| TC (mg/dL)      | −0.2  | 0.02    |
| HDL (mg/dL)     | −0.1  | 0.17    |
| LDL (mg/dL)     | 0.2   | 0.03    |
| 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.

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

| Spearman correlation | r     | p-Value |
|---------------------|-------|---------|
| CypA (ng/mL)        | 0.73  | < 0.001 |
| hsCRP (mg/L)        | 0.67  | < 0.001 |

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

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,
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

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**Table 8** Logistic regression analysis

| Variable       | Coefficient | Std. error | p    |
|----------------|-------------|------------|------|
| Age (y)        | −0.002      | 0.05       | 0.96 |
| CypA (ng/mL)   | 0.1         | 0.06       | 0.025
|                 |             |            |      |
| hsCRP (mg/L)   | 0.06        | 0.04       | 0.18 |
| MDA (nmol/mL)  | 0.187       | 0.06       | 0.005
|                 |             |            |      |
| TC (mg/dL)     | −0.05       | 0.02       | 0.045
|                 |             |            |      |
| TG (mg/dL)     | 0.02        | 0.007      | 0.008
|                 |             |            |      |
| HDL (mg/dL)    | −0.13       | 0.06       | 0.042
|                 |             |            |      |

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

*p < 0.05 is taken statistically significant.
to other studies. The increased lipid peroxidation (MDA) occurs as a consequence of oxidative stress when the balance between oxidant and antioxidant status is impaired. 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. 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.

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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**References**

1 Krisman MN. Coronary heart disease and risk factors in India - on the brink of an epidemic? Indian Heart J 2012;64(04):364–367
2 Herrington W, Lacey B, Sherliker P, Armitage J, Lewington S. Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res 2016;118(04):535–546
3 Bhat MA, Mahajan N, Gandhi G. Oxidative stress status in coronary artery disease patients. ILJBLR 2012;1:2250–3137
4 Suzuki J, Jin ZG, Meoli DF, Matoba T, Berk BC. Cyclophilin A is secreted by a vesicular pathway in vascular smooth muscle cells. Circ Res 2006;98(06):811–817
5 Satoh K, Fukushima Y, Sugimura K, et al. Plasma cyclophilin A is a novel biomarker for coronary artery disease. Circ J 2013;77(02):447–455
6 Jin ZG, Melarango MG, Liao DF, et al. Cyclophilin A is a secreted cytokine that promotes endothelial cell migration. J Biol Chem 2008;283(01):623–637
7 Zhu C, Wang X, Deimun J, et al. Cyclophilin A participates in the nuclear translocation of apoptosis-inducing factor in neurons after cerebral hypoxia-ischemia. J Exp Med 2007;204(08):1741–1748
8 Nigro P, Pompiillo G, Cagrogrosci MC. Cyclophilin A: a key player for human disease. Cell Death Dis 2013;4(10):e888–e888
9 Satoh K, Matoba T, Suzuki J, et al. Cyclophilin A mediates vascular remodeling by promoting inflammation and vascular smooth muscle cell proliferation. Circulation 2008;117(24):3088–3098
10 Satoh K, Nigro P, Matoba T, et al. Cyclophilin A enhances vascular oxidative stress and the development of angiotensin II-induced aortic aneurysms. Nat Med 2009;15(06):649–656
11 Weintraub NL. Understanding abdominal aortic aneurysm. N Engl J Med 2009;361(11):1114–1116
12 Nigro P, Satoh K, O’Dell MR, et al. Cyclophilin A is an inflammatory mediator that promotes atherosclerosis in apolipoprotein E-deficient mice. J Exp Med 2011;208(01):53–66
13 Rezanni R, Favero G, Stacchiotti A, Rodella LF. Endothelial and vascular smooth muscle cell dysfunction mediated by cyclophilin A and the atheroprotective effects of melatonin. Life Sci 2013;92(17–19):875–882
14 Seizer P, Schönberger T, Schött M, et al. EMMPRIN and its ligand cyclophilin A regulate MT1-MMP, MMP-9 and M-CSF during foam cell formation. Atherosclerosis 2010;209(01):51–57
15 Zaki MM, Mohsen M, Shaaban MA, Sedky RM. Study of serum levels of cyclophilin A in patients with coronary artery disease. QJM: Int J Med 2020;113(Issue Suppl 1):hca061.002
16 Hussain M, Mohammed E, El-Sherbeny A, Shehata A. Cyclophilin A: a novel biomarker for cardiovascular disease in patients with type 2 diabetes. Egypt J Intern Med 2019;31(04):416
17 Ohtsuki T, Satoh K, Omura J, et al. Prognostic impacts of plasma levels of cyclophilin A in patients with coronary artery disease. Arterioscler Thromb Vasc Biol 2017;37(04):685–693
18 Alfonso A, Bayón J, Gegunde S, et al. High serum cyclophilin C levels as a risk factor marker for coronary artery disease. Sci Rep 2019;9(01):10576
19 Yan J, Zang X, Chen R, et al. The clinical implications of increased cyclophilin A levels in patients with acute coronary syndromes. Clin Chim Acta 2012;413(7–8):691–695
20 Vinitha A, Kutty VR, Vivekanand A, et al. PPIA rs6850: A > G single-nucleotide polymorphism is associated with raised plasma cyclophilin A levels in patients with coronary artery disease. Mol Cell Biochem 2016;412(1–2):259–268
24 Yossef AA, Issa HA, Ahmad ES, Farag SE, Abd El Bar NA. Assessment of plasma level of cyclophilin A in type 2 diabetic patients suffering from vascular diseases. Benha Med J 2018;35(02):188–193.

25 Noshin TF, Ali MR, Banik S. Increased oxidative stress and altered serum macro-minerals and trace elements levels are associated with coronary artery disease. J Trace Elem Med Biol 2021;64:126707.

26 Khaki Khatibi F, Yaghoubi A, Zarghami N, Rahbani M, Babaei H. Evaluation of hs-CRP, antioxidant markers and MDA in patients of coronary artery disease (CAD) containing non-smokers and non-diabetics. J Cardiovasc Thorac Res 2011;2:13–18.

27 Uppal N, Uppal V, Uppal P. Progression of coronary artery disease (CAD) from stable angina (SA) towards myocardial infarction (MI): role of oxidative stress. J Clin Diagn Res 2014;8(02):40–43.

28 Mutlu-Türköğlu U, Akalin Z, İlhan E, et al. Increased plasma malondialdehyde and protein carbonyl levels and lymphocyte DNA damage in patients with angiographically defined coronary artery disease. Clin Biochem 2005;38(12):1059–1065.

29 Stocker R, Keaney JF Jr. Role of oxidative modifications in atherosclerosis. Physiol Rev 2004;84(04):1381–1478.

30 Guruprasad S, Rajasekhar D, Subramanyam G, Srinivasa Rao PVLN, Vanajakshamma V, Latheef K. High sensitivity C-reactive protein levels across spectrum and severity of coronary artery disease. J Clin Sci Res 2012;1(03):126–130.

31 Rashidinejad H, Moazanzadeh M, Mirshekarpoor H, Ebrahimi F. The relationship between HS-CRP serum levels with the results of cardiac perfusion SPECT imaging in patients with suspected coronary artery disease. Asian J Biomed Pharm Sci 2015;5(50):30–33.

32 Ramachandran S, Venugopal A, Kutty VR, et al. Plasma level of cyclophilin A is increased in patients with type 2 diabetes mellitus and suggests presence of vascular disease. Cardiovasc Diabetol 2014;13(01):38.