Cyclophilin A: a novel biomarker for cardiovascular disease in patients with type 2 diabetes

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Background and aims
Type 2 diabetes mellitus (DM) is a strong independent risk factor for coronary heart disease. Cyclophilin A (CyPA) is a protein secreted from vascular smooth muscle cells in response to reactive oxygen species. It is suggested that CyPA plays an important role in later stages of atherosclerosis and plaque rupture. It was demonstrated that plasma levels of CyPA are significantly higher in patients with coronary artery disease (CAD) in proportion to severity of disorder. Moreover, several studies have demonstrated a role of CyPA as a biomarker of CADs. Indeed studies revealed significantly higher plasma levels of CyPA in patients with CAD with type 2 DM.
Objective
To assess the severity of CAD among diabetic and prediabetic patients and predict future cardiovascular events.
Patients and methods
The study was conducted on 65 patients with CAD diagnosed by coronary angiography, stratified according to GRACE score into low/intermediate/high death risk categories and subdivided into diabetic, prediabetic, and nondiabetic, and 20 age-matched and sex-matched patients, who had normal angiography as a control group. Blood samples were collected for determination of glycated hemoglobin (HbA1c), serum creatinine, cardiac troponin, and CyPA level using double-antibody sandwich enzyme-linked immunosorbent assay technique.
Results
There were significantly higher levels of CyPA among patient group than control group ($P<0.001$). Moreover, significantly higher CyPA levels were detected in diabetic group when compared with normal and prediabetic groups ($P<0.029$). CyPA was positively correlated with HbA1c in all patients and with diabetic patients. HbA1c was negatively correlated with serum creatinine and positively with estimated glomerular filtration rate in prediabetic group and with systolic blood pressure in diabetic group. The number of occluded vessels was positively correlated with both CyPA and HbA1c. The diagnostic sensitivity and specificity of CyPA were 76.92 and 95%, respectively, at a cutoff value of more than 13 ng/ml.
Conclusion
CyPA can be used as an early predictor of CAD in patients with type 2 DM and also in prediabetic patients.

Keywords:
coronary heart disease, cyclophilin A, type 2 diabetes

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Introduction

Type 2 diabetes mellitus (DM) is a strong and independent risk factor for coronary artery disease (CAD) [1]. This association is so strong that a diagnosis of DM could be considered a CAD risk equivalent. Individuals with DM have between two and eight times higher rates of cardiovascular events, compared with nondiabetic controls [2]. More than 75% of all mortality in diabetic patients is the result of CAD [3].

During calorie excess, adipocytes undergo hypertrophy and their stromal vascular fraction becomes infiltrated with macrophages. These macrophages around dead adipocytes form 'crown-like structures,' associated with expression of cytokines, including tumor necrosis factor-α and interleukin-6 [4]. These changes have been shown to coincide with the onset of insulin resistance and provide a pathophysiological link between metabolic and vascular disease [5]. These pro-inflammatory and metabolic consequences of

obesity and insulin resistance result in endothelial dysfunction [6].

It has been reported that the plasma levels of high-sensitivity C-reactive protein, brain natriuretic peptide, D-dimer, and fibrinogen can predict the occurrence of cardiovascular events and progression. However, the plasma levels of these biomarkers are increased in inflammatory diseases, in addition to arteriosclerotic diseases. Thus, the search for a useful biomarker that can effectively predict the risk of future progression to more serious cardiovascular events still remains to be developed [7].

Cyclophilin A (CyPA) belongs to a group of proteins collectively known as immunophilins, which play vital roles in many biological conditions, including protein folding, T-cell activation, and cell signaling [8].

Various cell types have been described to secrete CyPA into the extracellular space. For example, CyPA is released by macrophages upon stimulation with high levels of glucose [9]. Moreover, the release of CyPA by vascular smooth muscle cells appears to highly promote the pathophysiology of vascular inflammation in abdominal aortic aneurysms, vascular restenosis, and atherosclerosis [10]. In addition, both activated platelets and hypoxic cardiomyocytes have been shown to secrete CyPA into the extracellular space [11].

It was demonstrated that the plasma levels of CyPA are significantly higher in patients with CAD in proportion to the severity of the disorder [12]. It was previously reported that the plasma levels of CyPA are significantly higher in patients with CAD with type 2 DM [13]. Indeed, several studies have demonstrated the role of CyPA as a biomarker of CADs [14–18]. Huang *et al.* [14] reported that the plasma levels of CyPA 1 month after AMI predict the prognosis of the patients.

In the present study, we aimed to investigate the effect of hyperglycemia on CyPA level in patients suspected to have CAD in comparison with age-matched and sex-matched normoglycemic individuals not suspected to have CAD.

Patients and methods

Study participants

This is a case–control study that was conducted on 65 patients undergoing coronary angiography for suspected CAD (being subdivided according to their GRACE score into low-risk, intermediate-risk, and high-risk patients); their ages ranged from 45 to 65 years. Patients were subdivided into three subgroups [normoglycemic (n=15), prediabetic (n=25), and diabetic (n=25)] according to the American Diabetes Association [19] guidelines, stating to consider DM when glycated hemoglobin (HbA1c) is more than or equal to 6.5%, consider prediabetes when HbA1c is more than or equal to 5.7% but less than or equal 6.4%, and consider being normal when HbA1c is below 5.7%. The patients were selected from the Cardiology Department in Ain Shams University Hospitals during the period from January to March 2019, in addition to 20 age-matched and sex-matched controls. The study was approved by the Ethics Committee for medical research.

All patients with valvular or congenital heart disease, or recent myocardial infarction were excluded from the study. Diabetes was assessed by recording HbA1c, whereas CAD was diagnosed by GRACE score and coronary angiography.

Methods

After an informed verbal consent, all individuals in this study were subjected to comprehensive history taking; physical examination; standard 12-lead ECG; coronary angiography; laboratory investigations assigned in GRACE score, including serum creatinine, HbA1c, and serum troponin; and serum CyPA using enzyme-linked immunosorbent assay (ELISA) technique.

Serum creatinine was performed using Beckman coulter AU 480 system by a modified rate Jaffé method. Estimated glomerular filtration rate (eGFR) was calculated using MDRD equation. Troponin I was assayed using two-step assay chemiluminescent microparticle immunoassay using Architect I 1000. HbA1c was assayed on the D10 dual program based on chromatographic separation of the analytes by ion exchange high-performance liquid chromatography. CyPA concentrations were measured using a double-antibody sandwich ELISA using a commercially available ELISA kit supplied by Korain Biotech Co. Ltd. (Shanghai, China).

Statistical analysis

IBM SPSS statistics (V. 25.0, 2018; IBM Corp., Chicago, Illinois, USA) was used for data analysis. Data were expressed descriptively as median and interquartile range for quantitative skewed data. Comparison between each two groups was done using Wilcoxon rank sum test for skewed data for dependent samples. P value less than 0.05 was

considered significant, *P* value less than 0.01 was considered highly significant, and *P* value more than 0.05 was considered nonsignificant. Furthermore, the diagnostic performance of the studied parameters was evaluated using receiver operating characteristic curve analysis, in which sensitivity % was plotted on the *y*-axis and 100-specificity on the *x*-axis. The best cutoff value (the point nearest to the upper left corner of the curve) was determined.

Results

Description of both clinical and laboratory data are shown in Tables 1 and 2, whereas the number of occluded vessels in all studied groups and the management are shown in Table 3.

The most important findings were that HbA1c was significantly higher in all patient groups (mean, 6.238 ±1.117), with *P* value less than 0.001.

Moreover, regarding CyPA level, it was significantly higher in patients than control, with mean of 29.515 ±24.883 and 7.1±3.547, respectively, with *P* value less than 0.001 (Table 2). Moreover, it was significantly higher in diabetic group compared with prediabetic one and normal participants, with *P* value 0.029, as shown in Table 4 and Fig. 1 as well.

Correlations between both CyPA and HbA1c and all studied parameters are shown in Table 5. The most important findings were that CyPA levels were positively correlated with HbA1c in diabetic group (r=0.536, P=0.006). Moreover, HbA1c was significantly positively correlated with systolic blood pressure in diabetic group (r=0.562, P=0.003). However, in the prediabetic group, there was a significant positive correlation between HbA1c and eGFR (r=0.443, P=0.026), whereas HbA1c was negatively correlated with serum creatinine in the same group. In Table 6, a significant positive correlation was found between number of occluded vessels and both CyPA levels and HbA1c, with *P* values of 0.003 and 0.015, respectively, among all groups.

In Table 7, it was shown that CyPA has 95% specificity and 76.92% sensitivity at cutoff value of more than 13, as shown also in Fig. 2.

Discussion

Importantly, plasma CyPA is significantly increased in patients with inflammatory diseases such as rheumatoid arthritis [20]. Furthermore, it was found that CyPA expression in mice is closely associated with the development of intimal thickening, aortic aneurysms, and atherosclerosis [21–23]. The secretion of CyPA is regulated by activation of Rho-kinase [24], which plays a crucial role in inflammation, vascular contraction, and the development of atherosclerosis [25,26]. Thus, it seems plausible that the plasma levels of CyPA may discriminate between patients at high or low risk for CAD.

The present study is a case–control study conducted on 65 patients undergoing coronary angiography for suspected CAD, who were subdivided according to their GRACE score into low-risk, intermediate-risk, and high-risk patients; their ages ranged from 45 to 65 years. Patients were subdivided into three subgroups: normoglycemic (n=15), prediabetic (n=25), and

Table 1 Demographic and clinical data and laboratory results of patients and control

	Groups [*n* (%)]			χ^2	
	Patients	Control	Total	χ^2	*P* value
Sex					
Male	36 (55.38)	8 (40.00)	44 (51.76)	1.450	0.229
Female	29 (44.62)	12 (60.00)	41 (48.24)		
DM					
No	36 (55.38)	20 (100.00)	56 (65.88)	13.544	<0.001*
Yes	29 (44.62)	0 (0.00)	29 (34.12)		
HTN					
No	16 (24.62)	20 (100.0)0	36 (42.35)	35.598	<0.001*
Yes	49 (75.38)	0 (0.00)	49 (57.65)		
Dyslipidemia					
No	31 (47.69)	20 (100.00)	51 (60.00)	17.436	<0.001*
Yes	34 (52.31)	0 (0.00)	34 (40.00)		
Smoking					
No	44 (67.69)	16 (80.00)	60 (70.59)	1.116	0.291
Yes	21 (32.31)	4 (20.00)	25 (29.41		

DM, diabetes mellitus; HTN, hypertension. *Means significant or highly significant.

Table 2 Description of laboratory data of patients and control groups

	Groups		*t* test	
	Patients	Control	*t*	*P* value
Age				
Range	42–65	44–65	1.418	0.160
Mean±SD	57.338±6.629	54.950±6.444		
SBP				
Range	90–210	100–190	0.908	0.366
Mean±SD	134.769±23.459	129.500±19.861		
DBP				
Range	50–120	60–100	0.431	0.668
Mean±SD	78.308±12.031	77.000±11.286		
HR				
Range	60–104	60–100	0.825	0.412
Mean±SD	75.877±9.479	73.800±10.986		
Create				
Range	0.5–2	0.3–1.5	0.978	0.331
Mean±SD	0.985±0.330	0.905±0.274		
eGFR				
Range	20–90	46–90	–0.173	0.863
Mean±SD	76.046±19.141	76.850±14.412		
GRACE score				
Range	31–114	31–107	2.470	0.016*
Mean±SD	74.046±16.824	63.200±18.289		
HBA1c				
Range	4.5–8.5	4–5.5	4.725	<0.001*
Mean±SD	6.238±1.117	5.025±0.451		
Cyclophylin				
Range	3–100	2–14	4.000	<0.001*
Mean±SD	29.515±24.883	7.100±3.597		

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, heart rate; SBP, systolic blood pressure. *Means significant or highly significant.

Table 3 Number of occluded vessels in all studied patient groups

	Groups [*n* (%)]				χ^2	
	Normoglycemic	Prediabetic	Diabetic	Total	χ^2	*P* value
OCC vessels						
Vessels 0	3 (20.00)	6 (24.00)	3 (12.00)	12 (18.46)	8.348	0.214
Vessels 1	8 (53.33)	6 (24.00)	7 (28.00)	21 (32.31)		
Vessels 2	4 (26.67)	9 (36.00)	8 (32.00)	21 (32.31)		
Vessels 3	0 (0.00)	4 (16.00)	7 (28.00)	11 (16.92)		
Recommendations						
PCI	9 (60.00)	11 (44.00)	14 (56.00)	34 (52.31)	7.766	0.457
Medical ttt	4 (26.67)	8 (32.00)	5 (20.00)	17 (26.15)		
CABG	0 (0.00)	5 (20.00)	5 (20.00)	10 (15.38)		
Surgical correction	1 (6.67)	1 (4.00)	1 (4.00)	3 (4.62)		
Control risk factors	1 (6.67)	0 (0.00)	0 (0.00)	1 (1.54)		

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

diabetic (*n*=25). They were selected from the Cardiology Department in Ain Shams University Hospitals. In addition, 20 age-matched and sex-matched individuals were included as a control group.

In the current study, we found that CyPA level was statistically significantly higher in patients proven to have CAD by angiography (29.515±24.883) than control (7.100±3.597), with a *P* value less than 0.001

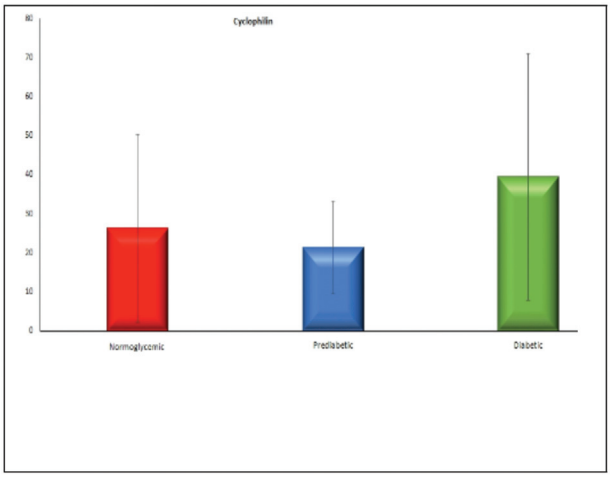
This was similar to a study done by Satoh *et al.* [27], who found that patients with high CyPA levels had a significantly higher prevalence of CAD by coronary angiography than those with low levels of CyPA.

Table 4 Comparison between cyclophilin A levels among all groups

Groups	Cyclophilin A		ANOVA	
	Range	Mean±SD	*F*	*P* value
Normal	3–100	26.333±23.924	3.748	0.029*
Prediabetic	3–45	21.440±11.906		
Diabetic	7.5–100	39.500±31.581		
Tukey's test				
N&PD	N&D	PD&D		
0.806	0.218	0.026*		

ANOVA, analysis of variance. *Means significant or highly significant.

Figure 1



Distribution of cyclophylin A level among the 3 studied groups.

We found that CyPA level was statistically significant higher in diabetic group in comparison with normoglycemic and prediabetic groups ($P<0.029$). In agreement with our results, Yossef *et al.* [28] found that there was a statistically highly significant increase in the median CypA concentration in all patient groups in comparison with the control group ($P<0.001$). Moreover, there was a statistically highly significant increase in the median CypA concentration in diabetic patients with CAD when compared with only diabetic patients group ($P<0.001$) and in patient with only CAD when compared with diabetic patients with or without CAD ($P<0.001$).

Ramachandran *et al.* [13] agreed with us and reported that patients with type 2 DM have higher circulating levels of CypA than the normal population. Plasma CypA levels were increased in patients with DM and CAD, suggesting a role of this protein in accelerating vascular disease in type 2 DM.

Yan *et al.* [29] also found that serum concentration of CypA in patients with acute coronary syndrome (UA and AMI) was significantly higher than those with

Table 5 Correlation between cyclophilin A and clinical and laboratory results, in addition to correlation between glycated hemoglobin and clinical and laboratory results

Pearson	HbA1c								Cyclophilin							
	Normoglycemic		Pre-DM		DM		Total		Normoglycemic		Pre-DM		DM		Total	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* Value	*r*	*P* value	*r*	*P* value
Age	−0.415	0.124	0.274	0.185	0.290	0.160	0.067	0.596	0.160	0.569	−0.079	0.707	0.084	0.689	0.102	0.419
SBP	0.053	0.850	−0.018	0.932	0.562	**0.003**	0.061	0.627	−0.026	0.926	−0.019	0.930	0.034	0.873	−0.021	0.869
DBP	0.275	0.321	−0.054	0.797	0.524	**0.007**	0.092	0.465	0.045	0.873	−0.207	0.321	−0.043	0.840	−0.094	0.457
HR	−0.139	0.621	0.249	0.230	−0.070	0.739	0.224	0.073	−0.021	0.942	0.037	0.859	0.051	0.809	0.080	0.526
Create	−0.143	0.611	−0.487	0.014	0.170	0.417	−0.086	0.494	−0.099	0.727	−0.055	0.795	0.265	0.201	0.048	0.706
eGFR	0.252	0.365	0.443	0.026	−0.219	0.292	0.043	0.732	0.127	0.652	0.095	0.651	−0.188	0.367	−0.051	0.685
GRACE score	−0.287	0.300	0.249	0.230	−0.073	0.730	−0.036	0.776	−0.108	0.703	−0.079	0.709	0.097	0.645	0.021	0.868
				HbA1c					−0.167	0.552	0.262	0.205	0.536	**0.006**	0.363	**0.003**

DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, heart rate; SBP, systolic blood pressure. Bold means highly significant data.

Table 6 Correlation between no. of occluded vessels and cyclophilin A and glycated hemoglobin

Spearman's rho	OCC. Vessels							
	Normoglycemic		Prediabetic		Diabetic		Total	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Cyclophilin	0.202	0.469	0.251	0.227	0.437	0.029*	0.359	0.003*
HbA1c	–0.202	0.471	0.325	0.113	0.063	0.764	0.301	0.015*

HbA1c, glycated hemoglobin. *Means significant or highly significant.

Table 7 Receiver operating characteristic for sensitivity and specificity of cyclophilin A

Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy
>13	76.92	95.00	98.0	55.9	90.5%

NPV, negative predictive value; PPV, positive predictive value.

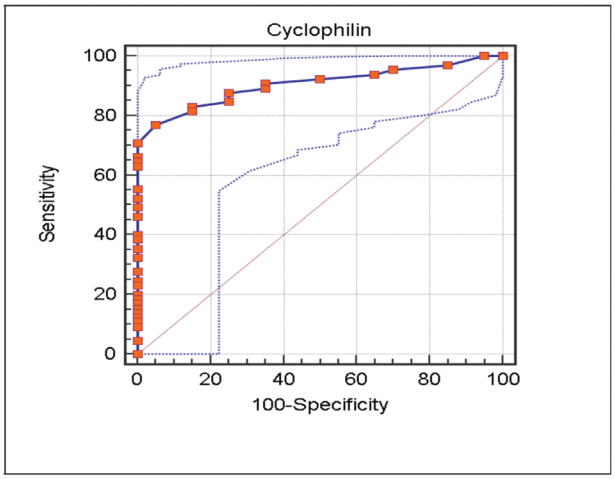
stable angina and controls ($P<0.05$). Hence, increased concentrations of CypA may be a valuable marker for predicting the severity of acute coronary syndrome.

A possible role for CyPA in atherosclerosis is becoming increasingly apparent. It was shown that knockdown of CyPA in EC reduced apoptosis, induced *in vitro* by tumor necrosis factor-α, and that CyPA deficiency was associated with a marked decrease in EC apoptosis in the early stages of atherosclerosis.

Our study revealed that CyPA level was significantly positively correlated with HbA1c, especially in the diabetic group. Other parameters such as age, systolic blood pressure, diastolic blood pressure, heart rate, serum creatinine, GRACE score, and eGFR had no significant correlation with CyPA among the studied groups.

On the contrary, Ramachandran *et al.* [13] reported that age was positively associated with increased plasma CypA level, whereas sex, serum levels of cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides were not associated with increase in CypA levels. In contrast, Satoh *et al.* [27] found that age, diabetes, and dyslipidemia correlated with plasma CypA levels in their patients with stenotic coronary arteries. Moreover, Ramachandran *et al.* [13] found that fasting blood glucose and HbA1c were positively associated with plasma CypA levels, indicating a specific relation of plasma CypA levels with hyperglycemia.In our study, we found that patients with 3-vessel disease were higher among diabetic patients in comparison with those with prediabetes and normoglycemic patients with CAD. We also found that CyPA level has a statistical significant positive correlation with the number of occluded vessels in patients with CAD ($P=0.003$). The findings of Satoh and colleagues go in line with our

Figure 2



Sensetivity and specificity of cyclophylin A level.

results, when they found that CyPA is a prognostic marker for requirement of cardiovascular intervention such as percutaneous coronary intervention and coronary artery bypass grafting. The increased severity of CAD observed among patients with elevated CyPA may be a consequence of a higher frequency of risk factors for atherosclerosis, all of which promote reactive oxygen species production and CyPA secretion. All these mechanisms, while promoting an environment of oxidative stress, are likely to contribute to the increased plasma levels of CyPA in patients with severe CAD [27].

Conclusion

It was demonstrated that CyPA level is increased in diabetic patients with CAD, and this could be of importance in both prevention and follow-up of type 2 diabetic patients with high cardiovascular risks.

Limitation

The small sample size has some limitation.

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Conflicts of interest
There are no conflicts of interest.

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