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Protein C Level in Type 2 Diabetic Patients with Ischemic Heart Disease

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ABSTRACT

Background: Diabetes Mellitus is among the most important risk factors for the development of cardiovascular diseases. Macro vascular complications associated with diabetes, namely, coronary artery disease, cerebro vascular disease and peripheral vascular disease are mainly due to accelerated atherosclerosis. The aim of this work was to assess the relationship of the level of protein C in diabetic patients with ischemic heart disease versus normal individuals.

Methods: case control study conducted on 90 with subjects who were classified into three equal groups: Group 1: diabetic patients without ischemic heart disease (normal coronary angiography). Group 2: diabetic patients with ischemic heart disease (with cardiac ischemia on coronary angiography). Group 3: Normal individuals as control.

Results: The mean Protein C level was highest in the Control group followed by DM without IHD group and lowest in DM with IHD group. Protein C demonstrated good diagnostic performance in discriminating between diabetes groups. Protein C achieved an AUC of 0.731 and an accuracy of 78.3%. The optimal cut-off value of 64 provided a sensitivity of 93.33% and a specificity of 63.33%.

Conclusions: Protein C levels were significantly lower in diabetic patients, especially those with ischemic heart disease (IHD), compared to healthy controls, linking Protein C deficiency to thrombotic complications. Multivariate analysis identified low Protein C levels and smoking as independent predictors of IHD severity. Protein C demonstrated strong diagnostic capability, indicating its potential as a useful biomarker for identifying vascular risk in diabetes..

Keywords: *Protein C Level, Type 2 Diabetic, Ischemic Heart Disease, Coronary Angiography*

1. INTRODUCTION

Diabetes Mellitus is among the most important risk factors for the development of cardiovascular diseases [1]. Diabetes and related complications are associated with long-term damage and failure of various organ systems [2]. Macro vascular complications associated with diabetes, namely, coronary artery disease, cerebro vascular disease and peripheral vascular disease are mainly due to accelerated atherosclerosis [3].

The patients with diabetes appear to have a higher prevalence of silent myocardial ischemia and asymptomatic CHD [4]. Macro and/or micro vascular complications are significant causes of the morbidity-mortality in diabetes and development of the haematological disorders in diabetes has been known for many years [5].

It has been shown in several studies that there is a tendency to hyper coagulability in diabetes. Hyun Kyung et al. has been found that, increase of coagulation factors (II, V, VII, VIII, X) and decrease of protein C levels in patients with diabetes [6].

There are increase in coagulation factors, and decrease in Protein C and hyper coagulation in diabetic patients. Mortality in the majority of patients with diabetes is considered to occur due to the coagulation mechanism disorders. Natural anticoagulants Protein C (PC) and its cofactor free Protein S F(PS) are likely to undergo changes in the process [7].

The aim of this work was to assess the relationship of the level of protein C in diabetic patient with ischemic heart disease

versus normal individuals.

2. PATIENTS AND METHODS:

This a case control study conducted on 90 with subjects who were admitted from outpatient and inpatient clinics of Specialized Medical Hospital, Mansoura University from July 2019 to July 2021.

The study protocol was reviewed and approved by the institutional review board of the faculty of medicine, Mansoura University, Egypt. Informed consent was waived by the board.

Inclusion criteria were adult subjects their age > 18 years old, both genders, suffering from type 2 diabetes and type 2 diabetes is diagnosed by either a fasting plasma glucose (FPG) level ≥ 126 mg/dl or a 2-hour plasma glucose level ≥ 200 mg/dl in an oral glucose tolerance test (OGTT) using a 75-g glucose load and Type 2 diabetes suffering from symptoms of ischemic heart disease admitted for coronary angiography.

Exclusion criteria were age < 18 years, Type 1 diabetes mellitus, history of chronic disease as patients with advanced liver disease, chronic renal failure, malignancy anywhere in the body and received anticoagulant medications.

The subjects were classified into three equal groups: Group 1: diabetic patients without ischemic heart disease (normal coronary angiography). Group 2: diabetic patients with ischemic heart disease (with cardiac ischemia on coronary angiography). Group 3: Normal individuals as control

3. METHODS:

All the studied cases were subjected to: Detailed history taking (Age, sex, Type and duration of diabetes, Treatment modality whether insulin or oral drugs or both controlled or not, Hypertension, the current medication, history of smoking or current smoker, family history of diabetes, hypertension and ischemic heart disease). Examination: General examination: Assessment of pulse, brachial blood pressure, systemic examination and foot assessment. Regional examination: Abdomen, neurological, Renal and chest examination. Cardiac examination: by palpation, percussion and auscultation of the heart. Anthropometric examinations to assess (Body mass index (BMI)). Laboratory investigations (Serum protein C, fasting plasma glucose, 2hours post prandial plasma glucose, HbA1c, lipid profile, serum creatinine, urine albumin creatinine ratio, INR). 12 lead electrocardiography (ECG). Coronary angiography.

Serum protein C was measured after using special and accurate precaution before, during and after sampling. these samples saved in special tubes containing Na citrate, protein c was measured from the collected samples by using CS 1600 device and special kits produced by Hyphen company.

12 lead electrocardiography (ECG): Routinely used to evaluate patients to detect any myocardial injury, ischemia or previous infarction [8].

Coronary angiography: coronary angiography was performed in all patients under local anesthesia via femoral artery using the Judkins technique. Multiple views were obtained in all patients with LAD and LCX coronary arteries visualized in at least 4 views and the RCA in at least 2 views by using (The radiographic equipment is of AXIOM Artis (FC/BC, AXA4-100.620.05.01.02), SIMENS, GERMANY with software; DICOM compliant).

Premedication: All patients were prepared for coronary angiography (4-6 hrs) fasting, shaving and preparation of both groins with an empty bladder. Sedation with diazepam 2.5-20 mg IV was given when clinically appropriate. Anti anginal medications (Calcium channel blockers, nitrate and beta blockers), hypolipedemic drugs were continued before coronary angiography as clinically indicated.

The Severity of CHD is determined by:

Vessel score:

which is the vessel number with significant stenosis. The 2011 American College of cardiology uses 50% stenosis to define significant vessel disease [9]. The range of score from 0 to 3, and it depended on the vessels involved. Left main artery stenosis was scored as single vessel disease [10].

Score 0 = no vessel involvement, score 1 = single vessel involvement, score 2 = double vessel involvement, Score 3 = triple vessel involvement

4. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS, Statistical Package. Qualitative data were represented as frequency and percentage. Quantitative data were presented as Mean Standard Deviations, Median, and IQR. A two tailed P value < 0.05 was considered significant.

5. RESULTS:

There was no significant difference between the diabetes groups and the control group as regard age, sex, BMI, special habits. In terms of HbA1c, the diabetes groups had significantly higher levels compared to the control group (p<0.001). For lipid profiles, the diabetes groups had significantly higher Total Cholesterol (p<0.001), Triglycerides (p<0.001), and LDL (p<0.001). Conversely, the control group had significantly higher HDL (p<0.001). For glucose levels, both fasting and postprandial glucose were significantly elevated in the diabetes groups (p<0.001). Similarly, Serum Creatinine was higher in the diabetes groups (p=0.022), but urinary ACR and INR did not show significant differences between groups (p=0.577). Protein C levels were significantly different between the diabetes groups and the control group (p<0.001). Table 1

Table 1: General Characteristics, Laboratory Investigations and Protein C level I of Diabetes Groups vs. Control

Parameter	Category	Diabetes Groups (n=60)	Control (n=30)	P value
Age (years)		58.48 ± 8.80	59.32 ± 2.64	0.990
Sex (%)	Female	20 (33.3%)	8 (26.7%)	0.687
	Male	40 (66.7%)	22 (73.3%)	
Body Mass Index (BMI)		28.16 ± 3.49	28.16 ± 0.86	0.998
Special Habits (%)	Non-Smoker	37 (61.7%)	19 (63.3%)	1.000
	Smoker	23 (38.3%)	11 (36.7%)	
HbA1c (%)		8.08 ± 1.40	5.03 ± 0.67	<0.001*
Urine Albumin-to-Creatinine Ratio (mg/g)		0.12 (0.05-0.20)	0.16 (0.06-0.22)	0.990
Total Cholesterol (mg/dL)		180.22 ± 40.77	141.90 ± 31.63	<0.001*
Triglycerides (mg/dL)		151.85 ± 72.07	103.60 ± 31.21	<0.001*
Low-Density Lipoprotein (LDL) (mg/dL)		113.50 ± 35.05	75.70 ± 13.87	<0.001*
High-Density Lipoprotein (HDL) (mg/dL)		39.47 ± 6.56	63.30 ± 13.18	<0.001*
Fasting Plasma Glucose (mg/dL)		182.78 ± 49.22	83.80 ± 9.81	<0.001*
2-Hour Postprandial Glucose (mg/dL)		277.77 ± 60.27	119.23 ± 11.78	<0.001*
Serum Creatinine (mg/dL)		1.02 ± 0.21	0.90 ± 0.14	0.022*
International Normalized Ratio (INR)		1.05 ± 0.07	1.02 ± 0.11	0.577
Protein C level (U/dL)		64.16 ± 28.57	100.80 ± 35.89	<0.001*

*Data is expressed as the mean ±SD or Median (IQR), *: significant P value <0,05*

Duration of Diabetes, medication, hypertension, hypertension Medication, family history of diabetes, family history of hypertension, and history of ischemic heart disease were insignificant difference between DM without IHD group. In Coronary Angiography, all patients in DM with IHD) group had stents (100%), whereas all patients in DM without IHD group had normal angiography results (100%). Table 2

Table 2: Clinical Data for Diabetes Groups

Parameter	Category	DM without IHD (n=30)	DM with IHD (n=30)	P value
Duration of Diabetes (years)		10.00 (5.00-20.00)	16.00 (10.00-20.00)	0.056
Medication	Oral	16 (53.3%)	13 (43.3%)	0.605
	Insulin	14 (46.7%)	17 (56.7%)	
Hypertension		27 (90.0%)	27 (90.0%)	1.000
Hypertension Medication	ACEI	20 (66.7%)	16 (53.3%)	0.420

	BB	7 (23.3%)	9 (30.0%)	
	CCB	0 (0.0%)	2 (6.7%)	
Family History of Diabetes		22 (73.3%)	25 (83.3%)	0.531
Family History of Hypertension		18 (60.0%)	22 (73.3%)	0.411
History of Ischemic Heart Disease		13 (43.3%)	14 (46.7%)	1.000
Coronary Angiography	Normal	30 (100%)	0 (0.0%)	<0.001*
	Stent	0 (0.0%)	30 (100%)	

*Data is expressed as the mean ± SD or Median (IQR), *: significant P value <0,05*

Regarding Protein C level, significant differences were observed among the study groups (p<0.001). The mean Protein C level was highest in the Control group followed by DM without IHD group and lowest in DM with IHD group. Statistical tests revealed significant differences between the groups (p<0.001). Pairwise comparisons showed statistically significant differences between all groups. In terms of HbA1c, Control group had significantly lower levels (5.03 ± 0.67%) compared to Groups 1 and 2 (p<0.001). For Total Cholesterol, the highest mean was in DM with IHD) group(195.27 ± 44.66 mg/dL), with Control group having the lowest (141.90 ± 31.63 mg/dL, p<0.001). Similarly, significant differences were noted for Triglycerides, LDL, HDL, Fasting Plasma Glucose, and 2-Hour Postprandial Glucose, where Control group consistently showed more favorable values except for HDL, which was highest in Control group. Serum Creatinine was slightly elevated in DM without IHD group compared to Groups 2 and 3 (p=0.024), while urinary ACR and INR did not show significant differences between groups. Table 3

Table 3: Protein C level and laboratory investigations in Study Groups

Parameter	DM without IHD (n=30)	DM with IHD (n=30)	Control (n=30)	P value	Pairwise Comparison
Protein C level (U/dL)	75.58 ± 36.46	52.73 ± 7.83	100.80 ± 35.89	p1<0.001*	p2<0.001* p3=0.040* p4=0.013*
HbA1c (%)	7.97 ± 1.41	8.19 ± 1.41	5.03 ± 0.67	p1<0.001*	p2=0.547, p3<0.001*, p4<0.001*
Urine Albumin-to-Creatinine Ratio	0.11 (0.04-0.20)	0.16 (0.06-0.23)	0.16 (0.06-0.22)	0.811	
Total Cholesterol (mg/dL)	165.17 ± 30.30	195.27 ± 44.66	141.90 ± 31.63	p1<0.001*	p2=0.012*, p3<0.001*, p4<0.001*
Triglycerides (TG) (mg/dL)	136.87 ± 47.99	166.83 ± 88.32	103.60 ± 31.21	p1<0.001*	p2=0.178, p3<0.001*, p4<0.001*
Low-Density Lipoprotein (LDL) (mg/dL)	101.00 ± 25.15	126.00 ± 39.29	75.70 ± 13.87	p1<0.001*	p2<0.001*, p3<0.001*, p4<0.001*
High-Density Lipoprotein (HDL) (mg/dL)	37.97 ± 6.05	40.97 ± 6.80	63.30 ± 13.18	p1<0.001*	p2=0.076, p3<0.001*, p4<0.001*
Fasting Plasma Glucose (mg/dL)	188.40 ± 55.00	177.17 ± 42.87	83.80 ± 9.81	p1<0.001*	p2=0.539, p3<0.001*, p4<0.001*

2-Hour Postprandial Glucose (mg/dL)	279.10 ± 67.67	276.43 ± 52.98	119.23 ± 11.78	p1<0.001*	p2=0.830, p3<0.001*, p4<0.001*
Serum Creatinine (mg/dL)	1.06 ± 0.22	0.98 ± 0.20	0.90 ± 0.14	p1=0.024*	p2=0.133, p3<0.001*, p4=0.211
International Normalized Ratio (INR)	1.05 ± 0.08	1.05 ± 0.06	1.02 ± 0.11	p1=0.845	

*Data is expressed as the mean ± SD or Median (IQR), *: significant P value <0,05, p1: comparison between all groups, p2: Comparison between DM without IHD groupand Group 2 (DM with IHD), p3: Comparison between DM without IHD groupand Control group, p4: Comparison between DM with IHD) groupand Control group*

Significant correlations were observed between Protein C levels and several parameters in diabetic patients. Negative correlations were noted with HbA1c, total cholesterol, triglycerides, LDL, fasting plasma glucose, and 2-hour postprandial glucose, all of which were statistically significant. A positive significant correlation was observed with HDL. Other parameters, including age, urine albumin-to-creatinine ratio, serum creatinine, INR, and BMI, showed no significant associations with Protein C levels. Table 4

Table 4: Correlations between protein C and study parameters in diabetic patients.

Variable	rs	P-Value
Age (years)	0.040	0.705
HbA1c (%)	-0.398	<0.001*
Urine Albumin-to-Creatinine Ratio (ACR) (mg/mmol)	-0.103	0.334
Total Cholesterol (mg/dL)	-0.419	<0.001*
Triglycerides (TG) (mg/dL)	-0.229	0.030*
Low-Density Lipoprotein (LDL) (mg/dL)	-0.459	<0.001*
High-Density Lipoprotein (HDL) (mg/dL)	0.256	0.015*
Fasting Plasma Glucose (mg/dL)	-0.412	<0.001*
2-Hour Postprandial Glucose (mg/dL)	-0.405	<0.001*
SerumCreatinine (mg/dL)	0.010	0.929
International NormalizedRatio (INR)	-0.123	0.249
Body Mass Index (BMI) (kg/m²)	-0.023	0.827

*rs: Spearman correlation coefficient, * for significant p value (<0.05),*

Protein C demonstrated good diagnostic performance in discriminating between diabetes groups. Protein C achieved an AUC of 0.731 and an accuracy of 78.3%. The optimal cut-off value of 64 provided a sensitivity of 93.33% and a specificity of 63.33%. Figure 1

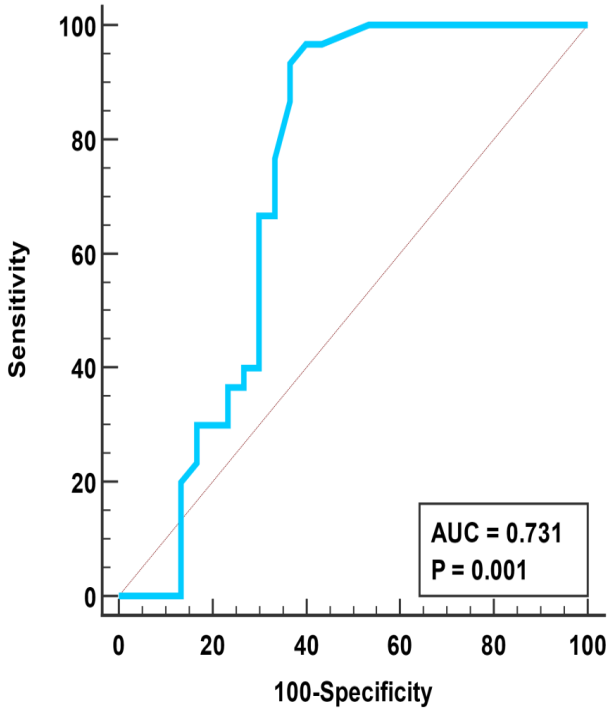

Figure 1: ROC curve of protein C in discrimination between diabetes groups.

The logistic regression analysis identified significant predictors of IHD severity in both univariate and multivariate models. In the univariate analysis, Protein C level, total cholesterol, low-density lipoprotein (LDL), and smoking were significant predictors. In the multivariate model, Protein C level ($p < 0.001$) and smoking status ($p = 0.048$) remained significant independent predictors. Table 5

Table 5: Logistic regression analysis for predictors of severity of IHD.

	Univariate				Multivariate			
Predictor	**B**	**CI_lower**	**CI_upper**	**p_value**	**B**	**CI_lower**	**CI_upper**	**p_value**
Protein C level	-0.085	-0.136	-0.048	<0.001*	-0.109	-0.171	-0.059	<0.001*
Total Cholesterol	0.023	0.008	0.041	0.008*	0.037	-0.001	0.083	0.092
Low-Density Lipoprotein	0.025	0.008	0.044	0.007*	-0.034	-0.090	0.013	0.200
Special Habits (Smoker)	1.340	0.226	2.529	0.022*	1.904	0.083	3.836	0.048*

6. DISCUSSION

Diabetes Mellitus is the most important risk factors for the development of cardiovascular diseases. Endothelial dysfunction and accelerated atherosclerosis that occur in diabetic patients, are thought to play a key role in the development of cardiovascular complications. Accelerated atherosclerosis is the most important factor in the development of microvascular complications in diabetic patients.[11].

In the current study, there was a significant and progressive decline in Protein C levels, observed from healthy individuals to diabetic patients without ischemic heart disease (IHD), and further to those with IHD. This trend suggests a potential role for Protein C deficiency in the development and progression of cardiovascular disease among diabetic patients.

The results of this study align with those of Kim et al., who compared 89 patients with diabetes to 49 healthy controls. The researchers reported a significant decrease in the levels of the anticoagulation factor protein Cin the diabetic patients compared to the controls [6]. Consistent findings were also reported by Katerina Thisiadou, who investigated 50 patients with type 2 diabetes and found significantly reduced levels of Protein C, Protein S, and Antithrombin III compared to controls

($p < 0.05$) [12].

In the current study, Protein C has shown a reasonable ability to differentiate between diabetic patients with and without ischemic heart disease (IHD). With a high sensitivity of 93.3%, it indicates potential as a biomarker for thrombotic risk in individuals with diabetes.

Our findings contradict those ofAktaş et al., who included 71 subjects: 50 were diabetic, 27 of whom also had diabetic neuropathy (DN), while 21 were non-diabetic. The researchers found no evidence to suggest that protein C and protein S levels could serve as markers for cardiovascular risk in diabetic neuropathic patients[13].

Multivariate logistic regression revealed that low Protein C levels were independent predictor of IHD severity. This underscores the role of Protein C deficiency in atherosclerotic disease progression among diabetic patients.

These findings align with the study conducted by Mahmoodi et al., which enrolled a total of 552 subjects from 84 different families in this retrospective family cohort study. The study reported that subjects with deficiencies in protein S or protein C, but not those with anti thrombin deficiency, had a higher risk of ATE before the age of 55. This increased risk was found to be independent of any prior episodes of venous thrombo embolism [14].

Regarding smoking in the current study Multivariate analysis identified smoking as independent predictor of IHD severity, our findings are consistent with those of Salehi et al., who included 11 studies with a total of 6,037 participants. Of these studies, six reported no relationship between smoking and the number of damaged arteries. One study indicated that smoking was associated with occlusion in the left anterior descending artery; however, there was no correlation found between smoking and the location of occlusions in other arteries. In contrast, five studies found that smoking was linked to the severity of CAD. Specifically, they reported an association between smoking, the severity of CAD, and the location of damaged arteries in the heart [15].

Regarding Protein C and Metabolic Parameters, In this study we identified significant negative correlations between Protein C levels and HbA1c ($rs = -0.398$, $p<0.001$), total cholesterol ($rs = -0.419$, $p<0.001$), triglycerides ($rs = -0.229$, $p=0.030$), LDL ($rs = -0.459$, $p<0.001$), fasting plasma glucose ($rs = -0.412$, $p<0.001$), and 2-hour postprandial glucose ($rs = -0.405$, $p<0.001$) in diabetic patients. These findings suggest that poorer glycemic and lipid control may reduce Protein C levels, potentially exacerbating thrombotic risk by impairing anticoagulation.

However, conflicting evidence exists. Ceriello et al. found no significant correlation between Protein C activity and HbA1c in non-insulin-dependent diabetic patients, suggesting variability across populations or disease stages [16].

Regarding Micro albuminuria in this study, Unexpectedly, our study found no significant differences in urine albumin-to-creatinine ratio (ACR) among diabetic patients with IHD, those without IHD and controls ($p=0.811$).

The literature predominantly supports an association between micro albuminuria and cardiovascular risk. Gerstein et al. (2001) in the HOPE study found micro albuminuria prevalent in 32.6% of diabetic patients and associated with a 1.97-fold increased risk of major cardiovascular events (95% CI, 1.68–2.31, $p<0.001$) [17].

Regarding HbA1c in this study therewas significantly elevated in diabetic patients ($p<0.001$), with no difference between those with and without IHD. However, its strong negative correlation with Protein C ($r=-0.398$, $p<0.001$) suggests that poor glycemic control may contribute to endothelial dysfunction and thrombosis risk.

In line with our findings, Addai-Mensah et al. conducted across-sectional study to evaluate the impact of poorly managed Type 2 Diabetes Mellitus (T2DM) on the levels and activity of Protein C (PC), Protein S (PS), and Antithrombin III (AT III). The study included 152 patients with poorly managed diabetes and 90 patients with well-managed diabetes. They discovered a negative correlation between HbA1c levels and the levels and activity of PC, PS, and AT III; specifically, higher HbA1c levels were associated with reduced Protein C levels. This suggests that chronic hyperglycemia, through non-enzymatic glycation of proteins, contributes to a prothrombotic state and may impair endothelial function[18]

Regarding coronary angiography in this study, all patients in the diabetic IHD group had stents, whereas those without IHD had normal angiography. This highlights the high burden of coronary artery disease in diabetic individuals and may further support the role of Protein C in thrombotic events.

Our results are consistent with the study conducted by Shrivastav et al., which compared the level of percent stenosis in coronary arteries of patients with coronary artery disease (CAD) both with and without type 2 diabetes mellitus (T2DM). The patients were divided into two groups: Group I included 100 patients with T2DM, and Group II consisted of 100 non-diabetic CAD patients who underwent coronary angiography using Judkin's technique. The study found a significant level of stenosis in the coronary arteries of CAD patients with diabetes[19].

Limitations: The single-center nature of the study may limit the generalizability of the findings to a broader population. Variations in healthcare practices, patient demographics, and environmental factors in different settings could influence the outcomes. The study case control included only 90 participants. The relatively small sample size may affect the statistical power of the study and limit the ability to detect subtle associations. The study design was case control, preventing the

establishment of a direct causal relationship between Protein C deficiency and ischemic heart disease in diabetic patients.

7. CONCLUSIONS:

Protein C levels were significantly lower in diabetic patients, especially those with ischemic heart disease (IHD), compared to healthy controls, linking Protein C deficiency to thrombotic complications. Poor glycemic control showed a negative correlation with Protein C, contributing to endothelial dysfunction and increased clotting risk. Dyslipidemia, characterized by elevated total cholesterol, LDL, and triglycerides, was more common in diabetic IHD patients. Multivariate analysis identified low Protein C levels and smoking as independent predictors of IHD severity. All diabetic IHD patients had coronary stents, reinforcing the high burden of coronary artery disease in diabetes. Protein C demonstrated strong diagnostic capability, indicating its potential as a useful biomarker for identifying vascular risk in diabetes.

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Conflict of Interest: Nil

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