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ORIGINAL ARTICLE

Low Protein Z Level: A Thrombophilic Risk Biomarker for Acute Coronary Syndrome

Manal Fawzy Ghozlan[1] · Amal Abd El-Hameed Mohamed[1] · Deena Samir Eissa[1] · Hassan Shehata Eldawy[2]

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Abstract Acute coronary syndrome (ACS) encompasses a range of thrombotic coronary artery diseases. Protein Z (PZ)/PZ-dependent protease inhibitor complex is a natural anticoagulant system with a presumptive role for PZ deficiency in the pathogenesis of ACS. We aimed to evaluate plasma PZ level and role as a risk biomarker in Egyptian patients with ACS. Hundred patients with stable ACS and 60 matched controls were enrolled. ACS patients were divided into 3 clinical subgroups (ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina), and 2 age subgroups (group A $\leq$ 55 years, and group B $>$ 55 years). Plasma PZ levels were evaluated using enzyme linked immunosorbent assay. Lower PZ levels were found in ACS patients' group and clinical subgroups compared with controls. PZ levels showed a decrease with increasing age and were lower in females versus males. Lower PZ levels were found in hypertensive ACS patients in both age subgroups. Smokers and patients with family history of ACS in group A had lower PZ levels, while group B revealed lower PZ among diabetic patients. In group A, increased number of ACS conventional risk factors was associated with lower PZ levels. PZ level 3.7 μg/mL was the best cut-off value for prediction of ACS. Logistic regression analyses approved PZ as an independent risk biomarker for ACS. PZ levels are reduced in stable ACS and are significantly and independently associated with increased susceptibility for ACS, denoting PZ deficiency as a reliable thrombophilic risk biomarker in Egyptian patients with ACS.

Keywords Acute coronary syndrome · Atherosclerosis · Protein Z · Protein Z-dependent protease inhibitor · Risk factor · Thrombosis

Introduction

Acute coronary syndrome (ACS) encompasses a range of thrombotic coronary artery diseases, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA), which are global life-threatening disorders and a major cause for emergency medical care and hospitalization [1]. In Africa and the Middle East, an alarming rise in the incidence of ACS at a younger age is promoted by the high prevalence of cardiovascular risk factors, resulting in a projected future burden of mortality that outstrip other geographical regions [2]. Thus, comprehensive understanding of the pathophysiology and identifying the risk factors, as well as exploring novel predisposing risk factors for ACS has become crucial for the proper prevention and treatment of ACS [3, 4].

Human protein Z (PZ) is a 62-kDa single-chain vitamin K-dependent glycoprotein, formed of 360 amino acids, and encoded by a 14-kb gene on chromosome 13q34. Liver is the main source for PZ, supported by the correlations between PZ and other plasma proteins of liver origin, and the severe deficiency of PZ in patients with liver disease [5–7]. Human endothelial cells were also found to synthesize PZ [8]. PZ is the last of vitamin K-dependent proteins to elute during anion exchange chromatography, thus it was named "Z" corresponding to the last character

✉ Deena Samir Eissa
dr.deena_samir@yahoo.com

[1] Department of Clinical Pathology, Faculty of Medicine, Ain Shams University, Ramses St., Abbassia, Cairo 11566, Egypt

[2] Department of Cardiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

of the alphabet [6]. PZ shares similar structure with other vitamin K-dependent factors VII, IX, X, and protein C, although lacks the proteolytic function [9–11].

PZ acts as a cofactor for the serine protease inhibitor, PZ-dependent protease inhibitor (ZPI), in the inactivation of phospholipid-bound FXa; PZ increases > 1000-fold the inhibition of FXa by ZPI. The main role for PZ/ZPI complex is to regulate early phases of coagulation cascade prior to the formation of prothrombinase complex [11, 12].

Clinical significance for low PZ on hemostatic system imbalance and thrombotic consequences arose from the finding that PZ knock-out mice showed increased risk for thrombosis after vascular injuries, and a severe thrombosis phenotype when combined with homozygous FV Leiden [9, 10, 13]. Nevertheless, studies addressing the mechanism for human PZ deficiency in the development of ACS, and the possible role for PZ level as a reliable risk biomarker for ACS reported conflicting debatable results. Accordingly, this study aimed to evaluate plasma PZ level and role as a risk biomarker in Egyptian patients with ACS.

Materials and Methods

This study was conducted on 100 Egyptian patients in stable phase of ACS; they had previous clinical history of ACS but were event-free over the last year prior to enrollment, recruited from the Cardiology Clinic, Ain Shams University Hospitals during the period May 2016 to September 2017. They were 78 males and 22 females (male to female ratio 3.5:1); ages ranged from 37 to 85 years (mean 56.6 ± 9.9 years). Patients with recent ACS, infections, chronic inflammatory diseases (C-reactive protein level [CRP] > 5 mg/L), cancers, liver dysfunction (positive hepatitis B or C viral markers and/or elevated liver function tests above the reference interval reported by the lab), renal disease (serum creatinine ≥ 1.5 mg/dL), intake of oral anticoagulants or hormonal contraceptives were excluded. Sixty age and sex-matched Egyptian healthy individuals were enrolled as a control group. They were 46 males and 14 females (male to female ratio 3.3:1); ages ranged from 35 to 75 years (mean 56.0 ± 9.2 years). All procedures were in accordance with the standards of the Ethical Committee for Human Experimentation of Ain Shams University and the Helsinki Declaration of 1964, as revised in 2002. An informed consent was obtained from all participants. The clinical and laboratory characteristics of ACS patients are illustrated in Table 1.

ACS patients were divided into three clinical subgroups: 51 patients with *STEMI*, 29 with *NSTEMI*, and 20 with *UA*. Moreover, as the age of > 55 years is associated with high risk for ACS [1], ACS patients were further divided into two age subgroups: *group A (≤ 55 years)*, 49 patients; and *group B (> 55 years)*, 51 patients.

Table 1 Clinical and laboratory characteristics of ACS patients

Parameters	ACS patients (n = 100)
Age (years)	
Mean ± SD	56.6 ± 9.9
Range	37–85
Gender, n (%)	
Male	78 (78)
Female	22 (22)
Hypertension[a], n (%)	58 (58)
Diabetes[b], n (%)	54 (54)
Dyslipidemia[c], n (%)	34 (34)
Smoking, n (%)	54 (54)
Family history[d], n (%)	41 (41)
ACS clinical subgroups, n (%)	
STEMI	51 (51)
NSTEMI	29 (29)
UA	20 (20)
ACS age subgroups, n (%)	
Group A, ≤ 55 years	49 (49)
Group B, > 55 years	51 (51)
Protein Z level (μg/mL)	
Mean ± SD	2.6 ± 1.0
Range	0.6–4.7

ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina

[a]Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, use of anti-hypertensive medications, or self-reported hypertension

[b]Diabetes mellitus is defined as non-fasting blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or hemoglobin A1c ≥ 6.5%, current use of antidiabetic medication, or self-reported diabetes

[c]Dyslipidemia is defined as LDL cholesterol ≥ 160 mg/dL, HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women, total/HDL cholesterol ≥ 4.0, or history of previous use of lipid-lowering medication

[d]Family history of ACS is defined by the presence of at least one first-degree relative developed ACS before the age of 55 years for men and 65 years for women [16]

Plasma PZ levels were assayed for patients and controls using ZYMUTEST Protein Z one-step enzyme linked immunosorbent assay for measuring human PZ (HYPHEN BioMed, Neuville-sur-Oise, France). Specimen collection and assay procedure for PZ were performed according to the manufacturer's instructions. Venous blood of 1.8 mL was collected in Vacutainer tube (Becton–Dickinson, NJ, USA) containing 0.2 mL of 3.2% tri-sodium citrate. Specimens were centrifuged at 2500×*g* for 20 min, plasma supernatant was decanted and stored frozen at − 70 °C

until PZ assay. The frozen plasma was thawed at 37 °C for 15 min and tested within 4 h. Briefly, the immunoconjugate; a polyclonal antibody specific for PZ coupled to horse radish peroxidase (HRP), was introduced into the microwells coated with a polyclonal antibody specific for PZ, followed by addition of the diluted plasma (1 plasma:50 dilution buffer). When present, PZ binds onto the polyclonal antibody-coated solid phase through one epitope, and fixes the polyclonal antibody coupled to HRP through free epitopes. Following a washing step, the peroxidase substrate tetramethylbenzidine, in the presence of hydrogen peroxide, was introduced and a blue color developed. When the reaction was stopped with sulfuric acid, a yellow color was obtained. The optical density, proportional to the concentration of PZ in the tested specimen, was measured at wave length 450 nm. Recombinant human PZ was used to generate a standard curve from which PZ concentrations of tested specimens were obtained, multiplied by the dilution factor (50×), and expressed in μg/mL. The intra-assay and inter-assay coefficients of variability are 3–8% and 5–10%, respectively.

Statistical Analysis

Statistical analysis was performed using Statistical Program for Social Science, version 20 (SPSS Inc., Chicago, Illinois, USA) on Windows 10 operating system. Categorical data were expressed in the form of frequency and percentage, while continuous data were expressed in the form of mean ± SD and range. Student *t* test was used for comparing continuous parametric variables between two groups. Correlation studies were performed using the Pearson correlation test (r). Receiver operating characteristic (ROC) curve and interactive dot diagram were applied to define the best cut-off value for PZ that could predict ACS with the best sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Uni- and multi-variate logistic regression analyses were performed (Odds ratio [OR] and 95% confidence interval [CI] were indicated) to evaluate the role for PZ as an established independent risk biomarker for ACS. p value < 0.05 and < 0.01 were considered significant and highly-significant, respectively.

Results

Protein Z Levels Among ACS Patients and Healthy Controls

Lower PZ levels were found in ACS patients (mean ± SD, 2.6 ± 1.0 μg/mL) and ACS clinical subgroups; mean ± SD, 2.5 ± 1.1, 2.6 ± 1.0, and 2.7 ± 1.1 μg/mL for STEMI, NSTEMI, and UA, respectively, compared with controls (mean ± SD, 4.9 ± 0.5 μg/mL) ($p < 0.001$ for each). However, no significant difference was found on comparing PZ levels among the different ACS clinical subgroups ($p = 0.783$) (Fig. 1).

Protein Z Levels in Relation to Age and Gender of ACS Patients

A negative correlation was found between PZ levels and patients' age (r = −0.739, $p < 0.001$). Lower PZ levels were found in group B (age > 55 years); mean ± SD, 1.9 ± 0.8 μg/mL, than group A patients (age ≤ 55 years); mean ± SD, 3.3 ± 0.8 μg/mL ($p = 0.001$) (Fig. 2). Reduced PZ levels were found in female (mean ± SD, 1.9 ± 0.8 μg/mL) compared with male patients (mean ± SD, 2.7 ± 1.0 μg/mL) ($p = 0.014$).

Protein Z Levels in Relation to Conventional Risk Factors for ACS in Group A and Group B Patients

In group A, lower PZ levels were found in ACS patients with hypertension, smoking, and family history of ACS compared with non-hypertensive, non-smoking patients, and those with no family history of ACS ($p = 0.042$, 0.037 and 0.027, respectively). A trend for lower PZ was detected among diabetic patients ($p = 0.06$). Patients with > 3 ACS conventional risk factors had lower PZ levels compared with patients having ≤ 3 risk factors ($p = 0.003$). No significant difference in PZ levels was found as regard other risk factors ($p > 0.05$) (Table 2). In group B, lower PZ levels were found in hypertensive and diabetic ACS patients compared with non-hypertensive, non-diabetic ones ($p = 0.004$, $p = 0.032$, respectively). However, PZ levels were comparable as regard other risk factors ($p > 0.05$) (Table 2).

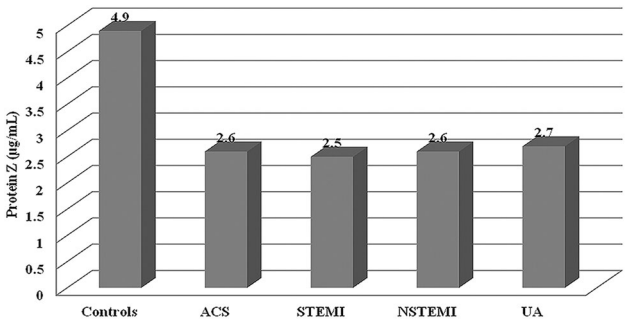

Fig. 1 Comparison of protein Z levels among ACS patients' group, clinical subgroups, and healthy controls. ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina

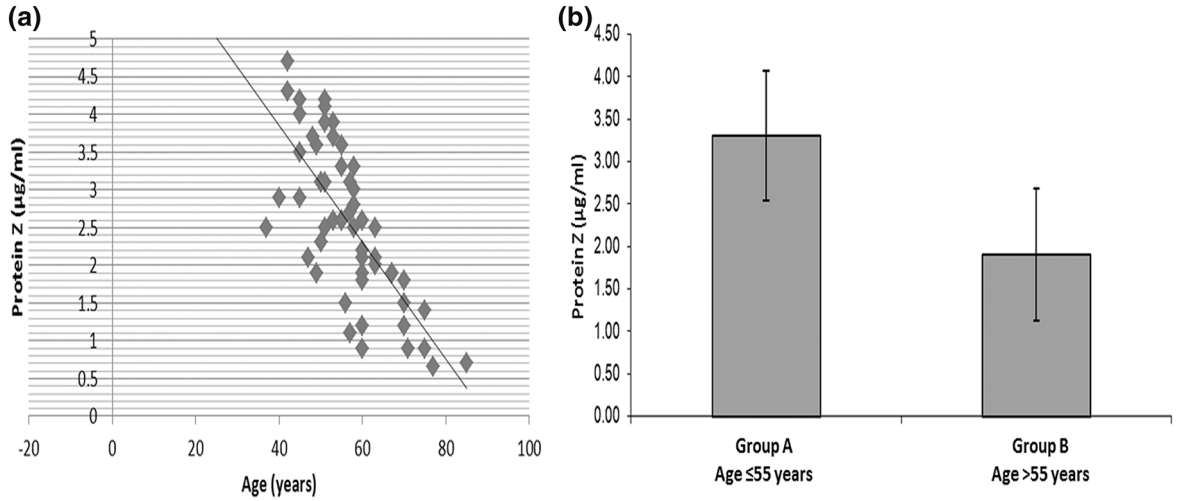

Fig. 2 Protein Z levels in relation to age of ACS patients. **a** Negative correlation between protein Z levels and age of ACS patients; **b** lower protein Z levels in group B than group A ACS patients. *ACS* acute coronary syndrome

Table 2 Protein Z levels in relation to conventional risk factors for ACS in group A and group B patients

Risk factors	Group A (n = 49)	PZ level (µg/mL) Mean ± SD	*p* value	Group B (n = 51)	PZ level (µg/mL) Mean ± SD	*p* value
Gender	Male (n = 41)	3.4 ± 0.8	0.101	Male (n = 36)	2.0 ± 0.8	0.14
	Female (n = 8)	2.7 ± 0.4		Female (n = 15)	1.5 ± 0.6	
Hypertension[a]	Yes (n = 27)	3.0 ± 0.6	0.042	Yes (n = 32)	1.6 ± 0.7	0.004
	No (n = 22)	3.6 ± 0.8		No (n = 19)	2.4 ± 0.6	
Diabetes[b]	Yes (n = 22)	3.0 ± 0.8	0.06	Yes (n = 32)	1.6 ± 0.7	0.032
	No (n = 27)	3.5 ± 0.6		No (n = 19)	2.3 ± 0.7	
Dyslipidemia[c]	Yes (n = 20)	3.1 ± 0.7	0.253	Yes (n = 14)	2.0 ± 0.8	0.485
	No (n = 29)	3.4 ± 0.8		No (n = 37)	1.8 ± 0.8	
Smoking	Yes (n = 25)	3.0 ± 0.7	0.037	Yes (n = 29)	2.1 ± 0.8	0.083
	No (n = 24)	3.6 ± 0.7		No (n = 22)	1.6 ± 0.7	
Family history[d]	Yes (n = 31)	3.1 ± 0.7	0.027	Yes (n = 11)	1.8 ± 0.6	0.825
	No (n = 18)	3.7 ± 0.7		No (n = 40)	1.9 ± 0.8	
Number of risk factors	≤ 3 Risk factors	3.8 ± 0.6	0.003	≤ 3 Risk factors	2.1 ± 0.8	0.704
	> 3 Risk factors	2.4 ± 0.4		> 3 Risk factors	1.2 ± 0.0	

ACS, acute coronary syndrome; PZ, protein Z

[a]Hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, use of anti-hypertensive medications, or self-reported hypertension

[b]Diabetes mellitus is defined as non-fasting blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or hemoglobin A1c ≥ 6.5%, current use of antidiabetic medication, or self-reported diabetes

[c]Dyslipidemia is defined as LDL cholesterol ≥ 160 mg/dL, HDL cholesterol < 40 mg/dL in men or < 50 mg/dL in women, total/HDL cholesterol ≥ 4.0, or history of previous use of lipid-lowering medication

[d]Family history of ACS is defined by the presence of at least one first-degree relative developed ACS before the age of 55 years for men and 65 years for women [16]

Diagnostic Validity for Protein Z Level in ACS

ROC curve and interactive dot diagram assigned 3.7 µg/mL as the best cut-off value for PZ that could predict ACS with 85.5% sensitivity, 100% specificity, 100% PPV, 78.9% NPV, and 0.981 area under curve ($p < 0.01$) (Fig. 3).

For the ACS clinical subgroups, ROC curve assigned 3.3 µg/mL as the best PZ cut-off value for predicting *STEMI* (85.7% sensitivity, 100% specificity, 100% PPV, 88.2% NPV, 0.976 area under curve, $p < 0.01$); 3.7 µg/mL for predicting *NSTEMI* (87.5% sensitivity, 100% specificity, 100% PPV, 93.7% NPV, 0.99 area under curve,

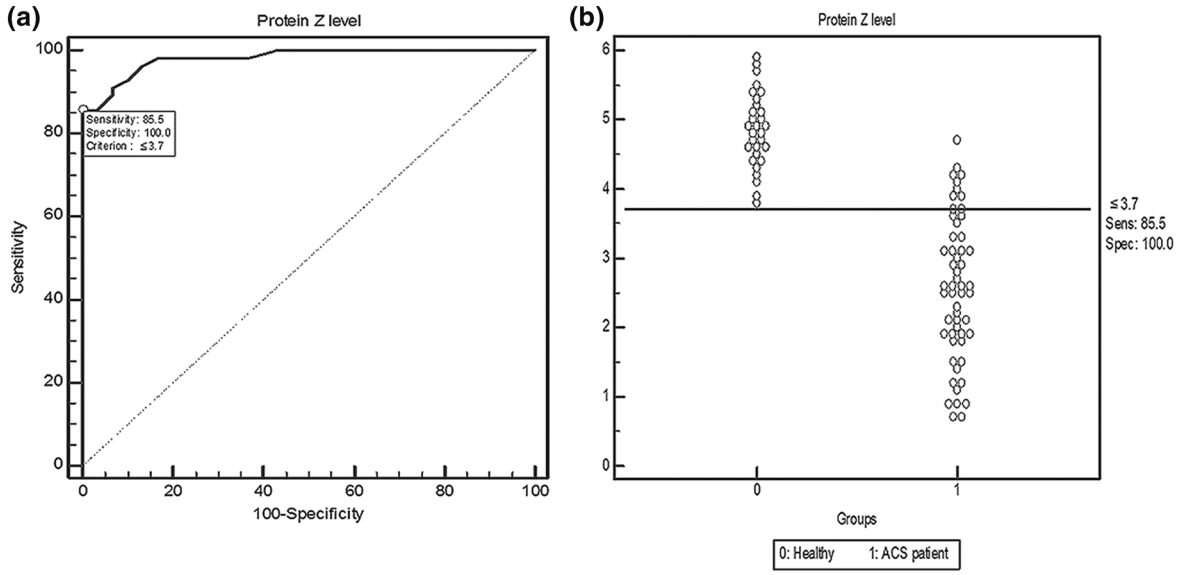

Fig. 3 Receiver operating characteristic curve (**a**) and interactive dot diagram (**b**) denoting the best cut-off value for protein Z in predicting ACS. *ACS* acute coronary syndrome

$p < 0.01$); and 4.2 μg/mL for predicting *UA* (100% sensitivity, 86.7% specificity, 73.3% PPV, 100% NPV, 0.983 area under curve, $p < 0.01$).

Role for Protein Z Level as an Established Independent Risk Biomarker for ACS

To perform the logistic regression analysis, we divided the study population into 2 groups according to our PZ cut-off value; one with ≤ 3.7 μg/mL, and the other with > 3.7 μg/mL, with the latter being the reference group. Uni-variate logistic regression analysis was performed using the 2 groups of PZ as the independent variable and ACS as the dependent variable, which revealed an increased risk for ACS with reduced PZ levels ≤ 3.7 μg/mL (OR 3.8; 95% CI 3.05–11.89; $p < 0.001$). Multi-variate logistic regression analysis was performed with the introduction of confounding variables for ACS represented by the studied conventional risk factors (age, gender, hypertension, diabetes, dyslipidemia, smoking, and family history), which showed an increased risk for ACS with low PZ levels ≤ 3.7 μg/mL after adjustment of the risk factors (OR 3.5; 95% CI 2.65–9.23; $p < 0.01$) (Table 3).

Discussion

Patients with recent ACS, infections, chronic inflammatory diseases, or cancers were excluded from our study to obviate increased consumption and inflammatory cytokines as possible causes for decreased PZ levels [14, 15]. Patients with liver or renal dysfunction were excluded to rule out decreased hepatic synthesis or renal loss as causes for low PZ levels [9, 11]. Moreover, PZ being a vitamin K-dependent protein, patients on warfarin therapy were excluded. Finally, as PZ has been reported to increase with the intake of oral contraceptives [9], female patients on hormonal contraception were excluded. In accordance, a study by Zhang and colleagues [16] addressed the impact of PZ in unexplained cerebral infarction in young and middle-aged adults and applied similar exclusion criteria to remove known or potential risk factors for cerebrovascular stroke, as well as to insure comparability of cases and controls.

In this study, we detected significantly lower PZ levels in stable ACS patients' group and clinical subgroups (STEMI, NSTEMI, UA) compared with healthy controls, however PZ levels were consistent among the ACS clinical subgroups. We constructed a ROC curve which assigned the PZ level 3.7 μg/mL as the best cut-off value for prediction of ACS. Moreover, PZ levels of 3.3, 3.7, and 4.2 μg/mL were assigned as the best cut-off values for predicting STEMI, NSTEMI, and UA, respectively.

Our findings agreed with a study performed in Italy by Sofi and coworkers [17] who reported speculative explanations for decreased PZ levels in ACS and denoted that PZ is known to be present in microvascular endothelial cells of atherosclerotic vessels suggesting its role in different phases of coronary atherosclerotic activity. Synthesis of PZ by endothelial cells could partly explain the direct link of PZ with endothelial dysfunction and atherosclerosis-related proinflammatory cytokines possibly downregulating PZ biosynthesis. Moreover, polymorphisms in the PZ gene might explain the influence of PZ in modulating atherosclerotic lesions apart from the acute thrombotic

Table 3 Logistic regression analysis for protein Z level as a risk biomarker for ACS

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
PZ > 3.7 μg/mL	Reference group		Reference group	
PZ ≤ 3.7 μg/mL	3.8 (3.05–11.89)	< 0.001	3.5 (2.65–9.23)	< 0.01

ACS, acute coronary syndrome; OR, Odds ratio; CI, Confidence interval; PZ, protein Z

event [17–19]. Moreover, a study by Pardos-Gea [20] denoted lower PZ levels in 110 patients with arterial and venous thrombosis compared with controls and reported an association between low protein Z levels and arterial thrombosis including acute myocardial infarction.

Unlike our findings, Refaai et al. [21] and Morange and Juhan-Vague [22] reported comparable PZ levels in ACS patients and controls. This contrast could be explained by the difference in time points of PZ assay; they prospectively measured baseline PZ concentrations in apparently healthy participants and followed them for the development of coronary events over a period of 9.7 ± 2.2 years and 5 years, respectively. They also did not confirm whether PZ assay was performed during the active or stable phase of ACS. Moreover, Liu et al. [10] although found consistent PZ levels among patients with stable ACS and controls, they detected significantly lower PZ levels among patients with active ACS compared with controls and patients with stable ACS. They proposed that low PZ during the active phase of ACS could be due to the consumption process caused by local activation of coagulation cascade, reinforced by the inverse correlation between PZ and D-dimer levels, as well as the inhibitory effect of inflammatory cytokines supported by the inverse correlation between PZ and high-sensitive CRP levels.

Additionally, discrepancy with other authors [10, 21, 22] has possibly been ascribed to the diversity of gene polymorphisms controlling PZ, able of modifying the circulating levels and resulting in interindividual variability and a wide range of normal PZ concentrations [23, 24]. Genetic and environmental factors have been suggested to influence plasma PZ levels. The human PZ gene is highly polymorphic; the single nucleotide polymorphism (SNP) database of the National Institutes of Health described 110 SNPs in the human PZ gene, and 14 SNPs in regions near PZ gene [13]. The A-13G polymorphism in the promoter region, G-103A in intron A, or G-79A in intron F of PZ gene are associated with reduced PZ level [13, 21, 24]. Interestingly, one study [25] reported lower levels of PZ in patients with ACS, despite a similar frequency of PZ polymorphisms between patients and controls, suggesting that PZ deficiencies observed were acquired, and could constitute a marker of vascular disease. Moreover, PZ being a vitamin K-dependent factor where vitamin K is known to be influenced by dietary intake, this could partly explain the wide distribution of PZ levels among the healthy population [6].

In this study, PZ levels in ACS patients showed significant decrease with increasing age. This could be explained by the decreased protein synthesis and the greater probability for vascular diseases associated with endothelial dysfunction that may modify synthesis or increase utilization/consumption of PZ with the aging process. Moreover, we showed significantly lower PZ levels in female than male patients which agreed with other authors [14, 21, 26] who suggested an influence of estrogen on PZ levels and a potential implication for PZ alterations in the occurrence of ACS in females. They reported that although the use of oral hormonal contraceptives is associated with higher plasma levels of PZ; however, physiological levels of estrogens are associated with lower concentrations of PZ in women than in men.

We revealed lower PZ levels in hypertensive ACS patients in both age groups. Other researchers [19, 27] showed lower PZ levels in hypertensive patients with peripheral arterial diseases. They reported that concurrent presence of low PZ levels and hypertension increased the susceptibility to peripheral arterial diseases which reinforces the involvement of low PZ levels in the pathogenesis of atherosclerotic disease. In contrast, Fedi et al. [14] did not find a significant relationship between hypertension and PZ levels in ACS.

In this work, group B showed lower PZ levels in diabetic patients, in addition to a trend for lower PZ levels among diabetics in group A. However, PZ levels were comparable among patients with and without dyslipidemia in both age groups. These findings agreed with those reported by Fedi and co-workers [14].

Smokers and patients with family history of ACS in group A showed significantly lower PZ levels. In accordance, a 9.5-fold increased risk for ACS in smokers with low PZ levels was reported [14]. The influence of smoking on PZ was suggested to arise from the wider involvement of inflammatory reactions secondary to the smoking damage [21, 27]. The relationship between low PZ and family history of ACS was attributed to the fact that atherosclerosis is a systemic longstanding degenerative process that

begins at early age, precipitated by risk factors, and manifested by early ACS [19].

Our study detected that among group A, the more the number of conventional risk factors for ACS, the lower the PZ levels. Similarly, increasing prevalence of PZ < 5th percentile among different numbers of traditional cardiovascular risk factors was reported [19]. For group B, old age is suggested to be the most powerful risk factor for decreasing PZ with no relationship to the number of other ACS risk factors.

However, Fedi and colleagues [14] could not find significant relationship between PZ levels and neither the family history nor the number of conventional risk factors for ACS. Moreover, Morange and Juhan-Vague [22] reported no association between PZ levels and any of the conventional cardiovascular risk factors. The variation between our study and these reports might be attributed to the difference in timing of PZ assay, various racial and ethnic backgrounds of the studied populations, and the diversity of gene polymorphisms controlling plasma PZ levels.

Finally, in accordance with other researchers [14, 17], logistic regression analyses revealed a significantly increased risk for ACS with reduced PZ levels, approving PZ as an established independent risk biomarker for ACS.

Conclusion

PZ levels are reduced in patients with stable ACS and are significantly and independently associated with increased susceptibility for ACS, denoting low PZ level as a reliable thrombophilic risk biomarker in Egyptian patients with ACS. This study adds further insights into the role for PZ in the pathogenesis and risk prediction of ACS and triggers the need for future long-term adequately-powered follow-up prospective studies to investigate PZ level along with its activity and genetic polymorphisms in relation to the prothrombotic state and in different phases of activity of ACS.

Limitations

The relation of low PZ level to non-traditional ACS risk factors including platelets and related parameters, as well as the potential contribution of other natural anticoagulants as protein C, protein S, and antithrombin in the pathogenesis of ACS remain unknown. These limitations represent an interesting area for future research.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval All procedures performed in this study were in accordance with the standards of the Ethical Committee for Human Experimentation of Ain Shams University and the Helsinki Declaration of 1964, as revised in 2002.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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