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ORIGINAL ARTICLE

Pregnancy-associated plasma protein-A (PAPP-A) as a possible biomarker in patients with coronary artery disease

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Abstract

Background Cardiovascular disease is the leading cause of death in the Western world, and a major cause of this disease is atherosclerosis. Research has demonstrated that pregnancy-associated plasma protein A (PAPP-A) plays a role in cardiovascular disease, as evidenced by the association between PAPP-A and severity of heart damage.

Aim The aim of this work was to investigate the correlation between PAPP-A concentrations in coronary and peripheral blood and certain clinicopathological factors and antioxidant enzyme activities in patients diagnosed with coronary artery disease.

Methods For 65 patients, arterial blood was obtained by puncturing the femoral or radial artery, and coronary blood was obtained via percutaneous coronary intervention. PAPP-A, catalase (CAT), superoxide dismutase-1 (SOD-1), and superoxide dismutase-2 (SOD-2) levels were measured using spectrometric methods.

Results Coronary PAPP-A levels were slightly higher than peripheral PAPP-A levels (81.25 ± 2.34 and 62 ± 3 ng/mL, respectively, $P < 0.0001$); these levels were correlated with each other ($r = 0.6629$, $P < 0.001$) but not with clinicopathological factors ($P > 0.05$). Coronary PAPP-A levels were significantly elevated among patients at risk for cardiovascular disease ($P < 0.05$). Antioxidant enzyme activities were significantly higher in coronary samples than in peripheral samples from subjects with ischemic cardiopathy secondary to atherosclerosis ($P < 0.001$). Neither coronary nor peripheral PAPP-A levels were correlated with antioxidant enzyme activities in patients with cardiopathy secondary to atherosclerosis ($P > 0.05$).

Conclusions PAPP-A levels could be used as biomarkers to identify patients at risk of coronary artery disease.

Keywords PAPP-A · Biomarker · Coronary artery disease

Introduction

Cardiovascular disease is the leading cause of death in the Western world, and its incidence has increased in recent decades. The major risk factors for coronary heart disease are cigarette smoking, heavy alcohol consumption, hypertension, hypercholesterolemia, diabetes mellitus, family history, physical inactivity, and obesity [1, 2]. Blood cholesterol is an important risk factor for coronary heart disease, and evidence exists to indicate that the main cause of cardiovascular disease is atherosclerosis [3, 4], a degenerative process that occurs in the vessel wall and leads to the progressive occlusion of the affected artery. It also involves inflammatory processes in different phases and stages [5]. Insulin-like growth factors (IGFs) I and II are secreted by cells of the cardiovascular system, and

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these factors promote the growth of arterial cells and act as mediators of cardiovascular diseases. Dysregulated actions of these factors contribute to atherosclerotic plaque development [6, 7]. IGFs, IGF receptors, and IGF-binding proteins (IGFBPs) are expressed in the heart, and their levels change locally following infarction. They participate in post-ischemic neovascularization and stimulate the reentry of adult ventricular myocytes into the cell cycle [8, 9].

Pregnancy-associated plasma protein A (PAPP-A) was first isolated in 1974 from the plasma of a pregnant woman [10]. PAPP-A cleaves IGFBPs; exerts specific proteolytic activity on IGFBP-2, IGFBP-4 and IGFBP-5; and has IGF-dependent cellular effects [11, 12].

Some studies have shown that PAPP-A plays a role in cardiovascular disease because of its association with the severity of heart damage. In 2001, Bayes-Genis and coworkers [13] showed, for the first time, the role of PAPP-A in acute coronary syndromes. They used immunohistochemistry to examine the levels of PAPP-A protein in eight culprit unstable coronary plaques and four stable plaques from eight patients who had died suddenly of cardiac causes. They also measured the circulating levels of PAPP-A, C-reactive protein (CRP), and IGF-I in 17 patients with acute myocardial infarction, 20 with unstable angina, 19 with stable angina, and 13 controls without atherosclerosis. This protein was overexpressed in plaque cells, the extracellular matrix in unstable plaques, and in patients with unstable angina or acute myocardial infarction. PAPP-A level was significantly and inversely associated with the extent of atherosclerosis. Moreover, PAPP-A protein expression was significantly correlated with CRP and free IGF-I. Subsequently, other studies revealed that PAPP-A levels are associated or correlated with markers of cardiovascular events: CRP, IGF-1, cardiac troponin I (cTnI), vascular endothelial growth factor (VEGF), interleukin-10 (IL-10), soluble CD40 ligand, creatine kinase-MB fraction (CK-MB), B-type natriuretic peptide (BNP), and OX40 ligand [14–33]. Accordingly, PAPP-A has been proposed as a possible mediator of the inflammatory reactions believed which lead to plaque rupture and clinical instability.

However, the question of whether coronary and/or peripheral PAPP-A levels are elevated or reduced in various patients remains unresolved. Evaluations of correlations involving PAPP-A levels could indicate whether this protein is a possible biomarker of cardiovascular diseases; in particular, researchers generally presuppose that an increase in a cardiac marker in the peripheral circulation is a reflection of this marker's liberation from coronary blood. In this respect, it has recently been demonstrated that C-reactive protein, myeloperoxidase, placental growth factor, and CD40 ligand measurements in systemic circulation were correlated with the corresponding measurements in coronary circulation in certain coronary diseases, including acute coronary syndrome and stable or unstable angina [34, 35]. In addition to addressing the possible role of PAPP-A in plaque instability, this work considers this protein as a biomarker for the diagnosis and early risk stratification in patients with suspected acute coronary ischemia, the presence of unstable plaques, and probable risk of myocardial injury. The objective of this study was to investigate the correlation between PAPP-A plasma concentration in samples of peripheral and coronary blood from patients diagnosed with coronary artery disease. In addition, we determined the differences in PAPP-A plasma concentration by comparing different clinical pathological factors and their correlations with body mass index (BMI), systemic blood pressure, glucose, cholesterol, triglycerides, CK-MB, cTnI, and BNP. Furthermore, we analyzed the correlation between PAPP-A plasma concentration and the activities of antioxidant enzyme markers in patients with cardiopathy secondary to atherosclerosis.

Subjects and methods

Biological samples

All samples were collected from the Interventional Cardiology Laboratory, Central Military Hospital, Secretaría de la Defensa Nacional (SEDENA) in Mexico City from patients who presented with symptoms of chest pain. Diagnoses followed the 2014 American College of Cardiology/American Heart Association Task Force on Practice Guidelines (2014 AHA/ACC guidelines). In brief, the patients were evaluated by reviewing medical records (patient history and physical examination), ECG changes, diagnostic coronary angiography results and laboratory analyses, including levels of the routine biomarkers CRP, c-cTnI, and myoglobin, creatine kinase (CK), CK-MB, and BNP. The patients were diagnosed with coronary artery disease and grouped as follows: ST-segment elevation myocardial infarction (STEMI) patients with prolonged chest pain; non-ST-elevation myocardial infarction (NSTEMI) patients with prolonged chest pain; unstable angina pectoris (UAP) patients; and stable angina pectoris (SAP) patients. This study included 65 samples of arterial blood obtained by puncturing the femoral or radial artery (peripheral blood) and 65 samples of coronary artery blood obtained via percutaneous coronary intervention (coronary blood) from patients. The 65 study subjects had a mean age of 70.08 ± 9.18 years and ranged from 48 to 83 years of age. Peripheral blood samples were obtained by puncturing the femoral or radial artery (with the initial

sample unused due to locally released biological factors) upon admission to the coronary care unit, prior to the administration of any medication. Once a peripheral blood sample was obtained, the patients underwent a coronary angiography. A wire guide and a 6 Fr introducer were placed, and a right or left coronary catheter was passed until the coronary ostium was cannulated. Contrast medium was injected to draw the coronary anatomy and thereby reveal or exclude coronary obstructions. Subsequently, a floppy guide wire was passed through this catheter until the distal third of the coronary artery was crossed, and a microcatheter (Progreat^{TM}, Terumo Medical Corporation, Somerset, NJ, USA) was passed beyond the obstruction. The floppy guide wire was then removed, and the coronary blood sample was obtained. Blood was collected and centrifuged within 30 min at $2000\times g$ for 15 min, and plasma was stored in aliquots at −80 °C until analysis. None of the assessed patients received heparin before sampling, because heparin administration has been associated with a significant increase in PAPP-A levels [36, 37]. However, immediately after the procedure, the patients were administered unfractionated heparin (70 IU/kg), and before the procedure, NSTEMI, UAP patients received 300 mg of acetyl salicylic acid and STEMI patients received 600 mg of acetyl salicylic acid. No thrombotic events were observed in recruited patients.

All samples were acquired for the PAPP-A analysis, and informed written consent to participation in this study was obtained. Sample collection was conducted from August 2013 to May 2015. Inclusion criteria (STEMI, NSTEMI, UAP, and SAP patients who were referred for percutaneous coronary intervention) and exclusion criteria (any active inflammatory condition or neoplastic disease, a thrombotic disorder, a history of major surgery or trauma within the prior month, pregnancy, and/or kidney or liver failure) were considered. Clinical pathological characteristics and biochemical parameters were measured. Ethical approval was provided by the Bioethics and Research committees under registration number DINV-79725. The human experimentation guidelines of these committees and the Declaration of Helsinki were followed.

Measurement of PAPP-A in plasma

PAPP-A levels were measured by applying a manual enzyme-linked immunosorbent assay (ELISA)-based spectrophotometric approach involving the use of PAPP-A Ultra Sensitive (US) Enzyme Immunoassay Kits (DRG Instruments GmbH, Marburg, Germany). These kits were designed to detect low concentrations of circulating enzymes associated with plaque destabilization. Briefly, an aliquot of 100 μL of a patient sample (containing endogenous PAPP-A) or standard was incubated in a well. After incubation, the well was rinsed, and 100 μL of conjugated enzyme was added and incubated for 60 min. After incubation, the unbound material was washed away. After two more incubations and two rinses, a complex was formed with a polyclonal biotinylated anti-PAPP-A antibody peroxidase conjugate (100 μL of enzyme complex and 100 μL of substrate solution). Subsequently, the enzymatic reaction was terminated with stop solution, and the absorbance was measured at 450 nm using a spectrophotometer (Synergy, BioTek Instruments, Winooski, VT, USA). The intensity of the color developed was proportional to the concentration of PAPP-A in the patient sample. The PAPP-A concentration was expressed in ng/mL of sample.

Determination of CAT, SOD-1, and SOD-2 in plasma

Superoxide dismutase (SOD) activity was determined using a competitive colorimetric inhibition assay, and catalase (CAT) activity was determined by examining the production of fluorescent resorufin from hydrogen peroxide. A non-fluorescent detection reagent was used, and a peroxidase reaction was performed using SOD and CAT activity kits (ENZO Life Sciences, Plymouth Meeting, PA, USA) according to the manufacturer's instructions.

Briefly, for SOD, samples or standards (25 μL) were incubated with 150 μL of reaction mixture containing WST-1 and xanthine oxidase, and xanthine solution was added. Formazan formation was measured at 450 nm. The addition of cyanide ions to a final concentration of 2 mM inhibited more than 90 % of SOD1 activity. SOD2 is unaffected by cyanide. For CAT, samples or standards (50 μL) were incubated with 1.5 μL of hydrogen peroxide, and 100 μL of reaction cocktail (detection reagent, horseradish peroxidase and reaction buffer) was added. Resorufin formation was measured with excitation at 570 nm and emission at 590–600 nm. For both the SOD and CAT measurements, a 96-well plate reader was used (Synergy, BioTek Instruments, Winooski, VT, USA). SOD and CAT activities were expressed as units per milligram of protein.

Statistical analysis

Data were expressed as the mean ± SD. The normality of the distributions was assessed using the Kolmogorov–Smirnov test. To identify differences in PAPP-A concentration between coronary and peripheral blood, we used Student's *t* test. To analyze correlations between PAPP-A concentrations in coronary and peripheral blood with sex, age, obesity/overweight, hypertension, tobacco use, alcohol use, presence of diabetes, history of heart disease, atherosclerosis, hyperglycemia, hypercholesterolemia, and

hypertriglyceridemia, the analysis of variance univariate test (ANOVA) was used, followed by Bonferroni correction. The correlations between PAPP-A concentrations in coronary and peripheral blood and age, BMI, systemic blood pressure, glucose, cholesterol, triglycerides, CK-MB, cTnI, and BNP levels, and antioxidant enzyme activities was investigated by a parametric Pearson test. All statistical analyses were performed using GraphPad Prism version 3.0 and SPSS version 10.0. The results were considered significantly different when the P values were lower than 0.05.

Results

Group analysis

The results shown in Fig. 1 indicate that coronary PAPP-A levels were slightly higher than peripheral PAPP-A levels (81.25 ± 2.34 and 62 ± 3 ng/mL, respectively, $P < 0.0001$).

The characteristics of the examined patients are presented in Table 1. Table 2 indicates that coronary PAPP-A levels were significantly elevated in older male patients (>60 years). In addition, coronary PAPP-A levels were significantly higher than peripheral levels in patients with hypertension, hypercholesterolemia, hypertriglyceridemia, and atherosclerosis without hyperglycemia who are smokers or alcoholics with history of heart disease. The absence or presence of diabetes or obesity/overweight in the patients did not change this tendency.

Figure 2 indicates that the enzyme activities of SOD1, SOD2, and CAT were significantly higher in coronary samples than in peripheral samples from subjects with ischemic cardiopathy secondary to atherosclerosis ($P < 0.001$). Coronary SOD1, SOD2, and CAT levels were 71 ± 14, 78 ± 13, and 71 ± 18 U/mg of protein, respectively, and peripheral SOD1, SOD2, and CAT levels were 40 ± 19, 18 ± 5, and 18 ± 4 U/mg of protein, respectively.

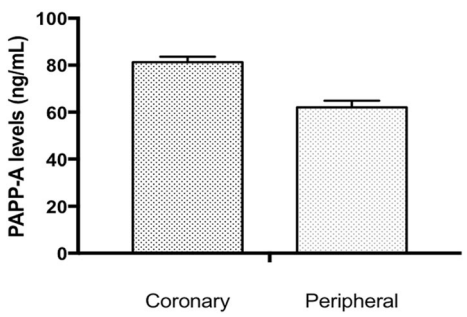

Fig. 1 Coronary and peripheral PAPP-A levels ($P < 0.0001$)

Table 1 Patients characteristics

Characteristic	*n*	%
Sex		
Male	34	52.3
Female	31	47.7
Age (years)		
<60	26	40
≥60	39	60
IMC (kg/m^2)		
<18.5	1	1.5
18.5–24.9	21	32.3
25–29.9	27	41.5
≥30	16	24.6
Blood pressure (mmHg)		
<120/<80	10	15.4
120–129/80–84	9	13.8
130–139/85–89	13	20
≥140/≥90	33	50.8
Tobacco use		
Yes	40	62.5
No	25	38.5
Alcohol use		
Yes	31	47.7
No	34	52.3
Diabetes		
Yes	38	58.5
No	27	41.5
History of heart disease		
Yes	25	38.5
No	40	61.5
Atherosclerosis		
Yes	35	53.8
No	30	46.2
Glucose (mg/dL)		
70–125	19	29.2
≥126	46	70.8
Cholesterol (mg/dL)		
<180	12	18.5
180–200	14	21.5
>200	39	60
Triglycerides (mg/dL)		
100–140	14	21.5
≥150	51	78.5

Correlation analysis

Peripheral PAPP-A levels showed a positive correlation with coronary PAPP-A levels ($r = 0.6629$, $P < 0.001$). As indicated in Table 3, no significant correlation was observed between either coronary or peripheral PAPP-A levels and age, BMI, systemic blood pressure, glucose,

Table 2 PAPP-A levels by sex, age, and medical history

Factor	Coronary		Peripheral		*P* value
PAPP-A level (ng/mL), mean ± SD					
Sex	Female	Male	Female	Male	
	61.77 ± 13.1	72.92 ± 2.34	45.88 ± 1.15	56.98 ± 1.24	<0.0001
Age (years)	<60	60	<60	60	
	55.39 ± 3.83	75.79 ± 2.39	45.47 ± 1.18	55.82 ± 2.9	<0.0001[a]
	Absent	Present	Absent	Present	
Obesity/overweight	66.47 ± 3.83	69.02 ± 5.57	52.53 ± 1.15	52.42 ± 3.33	<0.0001[b]
Hypertension	53.89 ± 3.88	72.89 ± 2.37	39.41 ± 1.23	56.38 ± 2.93	<0.0001
Tobacco use	62.39 ± 2.37	70.91 ± 3.83	49.43 ± 2.9	53.09 ± 1.15	<0.0001
Alcohol use	56.53 ± 2.5	79.81 ± 13.1	43.92 ± 1.5	60.19 ± 1.75	<0.0001[c]
Diabetes	71.78 ± 21.6	64.69 ± 2.25	51.93 ± 8.22	51.5 ± 1.15	<0.0001[d]
History of heart disease	64.98 ± 2.35	71.88 ± 3.83	48.99 ± 1.25	55.95 ± 1.24	<0.0001
Atherosclerosis	51.74 ± 3.85	81.25 ± 2.5	39.68 ± 1.17	61.97 ± 2.9	<0.0001
Hyperglycemia	77.97 ± 33.9	63.36 ± 2.33	54.15 ± 10.37	50.67 ± 1.5	<0.0001[e]
Hypercholesterolemia	55.88 ± 7.73	75.68 ± 8.77	37.73 ± 1.19	61.04 ± 3.76	<0.01
Hypertriglyceridemia	44.25 ± 2.34	74.05 ± 10	33.94 ± 1.25	56.56 ± 1.15	<0.001

[a] Except between coronary samples from patients of age <60 vs. peripheral samples from patients age >60

[b] Except between without obesity/overweight group in coronary sample vs. obesity/overweight group in coronary sample and without obesity/overweight group in peripheral sample vs. obesity/overweight group in peripheral sample

[c] Except between without alcohol-use group in coronary sample vs. alcohol-use group in peripheral sample

[d] Except between without diabetes group in coronary sample vs. diabetes group in coronary sample and without-diabetes group in peripheral sample vs. diabetes group in peripheral sample

[e] Except between hyperglycemia group in coronary samples vs. without hyperglycemia group in peripheral samples and without-hyperglycemia group in peripheral sample vs. hyperglycemia group in peripheral sample

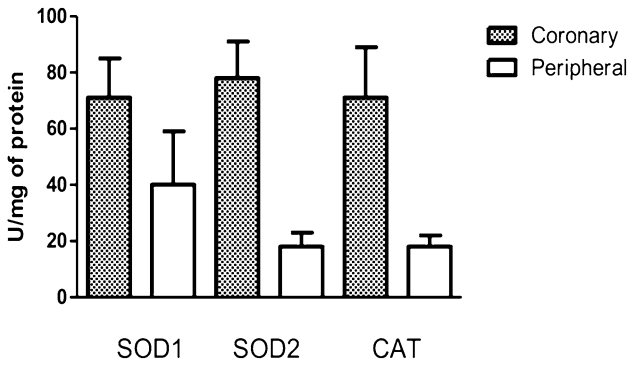

Fig. 2 Enzyme activities of SOD1, SOD2 and CAT in coronary and peripheral blood from subjects with cardiopathy secondary to atherosclerosis. All comparisons revealed significant differences ($P < 0.0001$), with the exceptions of SOD1 vs. SOD2, SOD1 vs. CAT, and SOD2 vs. CAT in coronary samples and SOD2 vs. CAT in peripheral samples ($P > 0.05$)

cholesterol, triglycerides, BNP, CK-MB, and/or cTnI levels ($P > 0.05$).

Finally, as indicated in Table 4, no correlation was found between coronary or peripheral PAPP-A levels and SOD1, SOD2, or CAT antioxidant activities in subjects with cardiopathy secondary to atherosclerosis ($P > 0.05$).

Discussion

The major findings of this study are as follows: (1) Coronary and peripheral levels of PAPP-A were positively correlated; (2) Coronary PAPP-A levels were significantly elevated among patients with certain risk factors for cardiovascular disease; and (3) Coronary antioxidant enzyme activities were higher than the corresponding peripheral activities in patients diagnosed with coronary artery disease and atherosclerosis.

Patients with cardiovascular disorders generally exhibit known risk factors, such as smoking, obesity, physical inactivity, high cholesterol, high blood pressure, high blood glucose, and/or the presence of atherosclerosis [2]. Research has demonstrated that circulating levels of PAPP-A, a zinc-binding metalloproteinase, are elevated in patients with acute coronary syndromes and patients with risk factors, such as obesity, hypertension, and/or diabetes, relative to healthy subjects [30, 38]. In acute coronary syndrome patients, PAPP-A has been found to be highly expressed in vulnerable atheromatous plaques [39–41]. In our study, coronary PAPP-A levels were significantly higher in older male patients with hypertension, hypercholesterolemia, and hypertriglyceridemia who had

Table 3 Correlation of PAPP-A levels with clinic parameters

Factor	Coronary		Peripheral	
	r	*P*	*r*	*P*
PAPP-A levels (ng/mL)				
Age (years)	−0.3664	0.0716	0.1378	0.5513
BMI (kg/m^2)	−0.2378	0.2523	0.005	0.9824
Blood pressure (mmHg)	−0.2689	0.2039	0.1387	0.5487
Glucose levels (mg/dL)	−0.2196	0.3024	−0.1149	0.62
Cholesterol levels (mg/dL)	0.079	0.7144	0.1942	0.3990
Triglyceride levels (mg/dL)	0.074	0.7330	−0.1305	0.5727
CK-MB levels (ng/mL)	−0.2669	0.3566	0.5734	0.254
cTnI levels (ng/mL)	−0.3548	0.3488	0.9547	0.1
BNP levels (pg/mL)	0.4274	0.1898	−0.2059	0.5208

Table 4 Correlation of PAPP-A levels with antioxidant enzymes activities of patients with cardiopathy secondary to atherosclerosis

Enzyme	Coronary		Peripheral	
	r	*P*	*r*	*P*
PAPP-A levels (ng/mL)				
SOD1 activity (U/mg protein)	−0.1748	0.4032	0.2137	0.3522
SOD2 activity (U/mg protein)	0.037	0.8579	0.1234	0.5942
CAT activity (U/mg protein)	0.1880	0.3683	−0.3044	0.3361

atherosclerosis and were smokers or alcoholics, although we did not observed correlations between coronary and peripheral PAPP-A levels and age, BMI, systemic blood pressure, glucose, cholesterol, or triglycerides. These results are consistent with those reported previously. In 2004, Cosin-Sales and coworkers demonstrated that PAPP-A levels are higher in men than in women diagnosed with coronary artery stenosis. In this study, we also found complex lesions in 60 % of men. [40]. The same author in 2005 and Elesber and coworkers in other studies showed that PAPP-A levels were significantly higher in hypertensive patients diagnosed with coronary atherosclerosis and atheromatous plaque disruption, and these elevated levels may have contributed to the transformation of stable atherosclerotic plaques into unstable plaques in patients with coronary disease [20, 42, 43]. In other studies, PAPP-A was found to be correlated with age, cholesterol, glucose, and triglyceride levels, and PAPP-A was found to be selectively expressed in unstable plaques in subjects with cardiovascular disease [22, 41, 44–46]. In our study, 35 subjects of the analyzed patients presented with cardiopathy secondary to atherosclerosis; this condition may have explained the slightly elevated coronary PAPP-A levels observed among these subjects. Atherosclerosis is a systemic chronic inflammatory disease, and the release of matrix metalloproteinases by macrophages within a stable plaque has been implicated in the transformation of stable plaques into unstable plaques [47]. Although it has been shown that circulating PAPP-A levels are slightly higher in patients with unstable plaques [48] in comparison with those with stable plaques, it has not been demonstrated that PAPP-A levels can be a useful predictive marker of plaque instability. We wanted to determine whether PAPP-A coronary levels were higher or lower in peripheral circulation and whether they are correlated with plaque instability. Our work showed a slight increase in coronary blood, in comparison with peripheral blood, although these levels correlated with each other. In accord with our results, we speculate that the marker is mainly produced from occluded coronary plaques but also possibly released from vulnerable coronary plaques. PAPP-A could also be carried from coronary to systemic circulation. The results of this study suggest that PAPP-A could be: (a) a marker of plaque remodeling rather than of plaque disruption; (b) used to evaluate the progression of coronary disease secondary to atherosclerosis; and (c) used in the detection of coronary atherosclerotic lesions in patients with cardiovascular risk, such as the patients in this study.

Increased oxidative stress is associated with the pathogenesis of coronary artery disease and with the initiation and progression of atherosclerosis. The generation of oxidative stress may induce vascular disorders and contribute to atherosclerotic plaque formation [49–51]. We showed that in coronary blood, SOD and CAT activities were increased in subjects diagnosed with ischemic cardiopathy secondary to atherosclerosis, compared with those

in peripheral blood. The levels were probably elevated to prevent lipid peroxidation and nitric oxide formation in the plaque [52, 53]. However, we also observed that SOD and CAT activities are not related to PAPP-A concentrations in these patients. This result suggests that reactive oxygen species have no role in the regulation of PAPP-A expression.

In the present work, we demonstrated for the first time that coronary PAPP-A levels are correlated with peripheral PAPP-A levels and that coronary and peripheral PAPP-A levels are not positively correlated with CK-MB and cTnI levels. In some studies, PAPP-A levels were not found to be related to the concentrations of cTnI or CK-MB [15, 16, 54], whereas in others, PAPP-A levels were found to be correlated with CK, cTnI, or BNP levels [14, 17, 26, 32, 46] in the context of coronary heart diseases (acute myocardial infarction, acute coronary syndromes or stable angina). Currently, myocardium biomarkers detect only necrosis, and patients with subocclusion or lysis of the thrombus cannot be diagnosed using these markers [24]. Elevated cTn and CRP are associated with an increased risk of further cardiovascular events, and CK-MB and cTn are currently the most sensitive and specific biomarkers of myocardial damage and necrosis [55]. In this study, we demonstrated that peripheral and coronary concentrations of PAPP-A are not significantly correlated in patients with biochemical evidence of cardiac damage.

In acute coronary syndromes, recent investigations have indicated that increases in biomarkers related to vascular inflammation, such as proinflammatory cytokines, plaque destabilization, plaque rupture, acute phase reactants, ischemia, necrosis, or myocardial dysfunction can be used to evaluate the overall patient risk and identify patients at higher risk of an adverse event. Although consolidated recognized biomarkers, such as CRP, cytokines, and adhesion molecules (CAMs), participate in the inflammatory process or plaque instability, it has been shown that PAPP-A is a possible reliable marker that can discriminate between cases of myocardial infarction from unstable angina and healthy people [56, 57]. Considering our results, PAPP-A levels are not related to the biomarkers of myocardial damage and necrosis, meaning that this marker could be an independent biomarker used to evaluate cardiovascular risk or that it could be used to add information to that provided by other markers, particularly in patients in whom markers of myocardial damage are not elevated. However, we recognize that is necessary to determine the exact mechanism underlying the correlation between PAPP-A and coronary plaque vulnerability.

Conclusions

Coronary PAPP-A levels are correlated with peripheral levels and coronary PAPP-A levels are significantly higher in patients with elevated cardiovascular risk. Patients with cardiopathy secondary to atherosclerosis likely show increased oxidative stress in coronary samples relative to peripheral samples. Peripheral PAPP-A levels could be used as biomarkers to identify patients at risk of developing coronary artery disease.

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Compliance with ethical standards

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Conflict of interest No author received a grant or speaker honorarium from any company. No author is a member of any committee. Hugo Gutiérrez-Leonard declares that he has no conflict of interest. Emmanuel Martínez-Lara declares that he has no conflict of interest. Alfonso E. Fierro-Macías declares that he has no conflict of interest. Victoria M. Mena-Burciaga declares that she has no conflict of interest. María D. Ronquillo-Sánchez declares that she has no conflict of interest. Esaú Floriano-Sánchez declares that he has no conflict of interest. Noemí Cárdenas-Rodríguez declares that she has no conflict of interest.

Ethical approval All procedures performed in this study were conducted in accordance with the ethical standards of the Bioethics and Research Committees of the Hospital Central Militar, SEDENA, Mexico City (Registration Number DINV-79725) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants in this study.

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