

PREGNANCY-ASSOCIATED PLASMA PROTEIN (PAPP-A) AS A PROGNOSTIC INDICATOR IN ACUTE CORONARY SYNDROMES

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PREGNANCY ASSOCIATED PLASMA PROTEIN (PAPP-A) U PROCENI RIZIKA KOD PACIJENATA SA AKUTNIM KORONARNIM SINDROMOM

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ABSTRACT

Despite diagnostic and therapeutic advances for acute coronary syndromes (ACS), the rate of event recurrence is still relatively high, and short- and long-term prediction of risk is necessary, although extremely challenging, to provide optimal treatment to patients. New markers of coronary artery disease progression have been identified in recent years, among which circulating levels of pregnancy-associated plasma protein-A (PAPP-A) offer an interesting profile. This protein is expressed in eroded and ruptured atheromatous plaques, and circulating levels are elevated in ACS. Available data indicate the use of PAPP-A as a prognostic marker in patients with ACS in addition to other prognostic factors, including C-reactive protein (CRP) and troponin levels. Simultaneous determination of biomarkers with distinct pathophysiological profiles appears to remarkably improve risk stratification in patients with ACS.

Keywords: Pregnancy-associated plasma protein A, acute coronary syndromes

SAŽETAK

Uprkos savremenim dijagnostičkim i terapijskim metodama, stopa neželjenih događaja je i dalje visoka kod pacijenata sa akutnim koronarnim sindromom, stoga je nepohodna bolja procena kardiovaskularnog rizika. Poslednjih godina otkriveni su novi biomarkeri za procenu progresije koronarne bolesti, među kojima je i pregnancy-associated plasma protein-A (PAPP-A). Pregnancy-associated plasma protein-A (PAPP-A) je izolovan u rupturiranim aterosklerotskim plakovima i nalazi se u povišenoj koncentraciji u krvi pacijenata sa akutnim koronarnim sindromom. Rezultati dosadašnjih studija pokazali su da je PAPP-A koristan marker u proceni kardiovaskularnog rizika kod pacijenata sa akutnim koronarnim sindromom zajedno sa C-reaktivnim proteinom i troponinima.

Uporedno određivanje različitih biomarkera značajno poboljšavaju stratifikaciju rizika kod pacijenata sa akutnim koronarnim sindromom.

Ključne reči: Pregnancy-associated plasma protein A, akutni koronarni sindrom



INTRODUCTION

Coronary atherothrombotic disease (CAD) often results in serious adverse cardiovascular (CV) events, despite aggressive treatment. These future events are usually due to thrombus formation at the site of a ruptured or eroded atherosclerotic plaque, and they are characterized clinically as acute coronary syndrome (ACS) (1). There is solid evidence that has established CV risk factors, including dyslipidemia, smoking, hypertension and diabetes mellitus, which can be incorporated into algorithms for risk assessment in the general population (2). It is well known, however, that these characteristics do not fully explain CV risk (3). Measurements of cardiac biomarkers might, therefore, independently predict risk beyond conventionally used stratification tools and may also give a reliable indication of CV risk in patients with ACS (4,5).

The elevation of biomarkers indicates the onset of several harmful mechanisms that place the individual patient in a high-risk category.

THE PREGNANCY-ASSOCIATED PLASMA PROTEIN A (PAPP-A): A NOVEL AND PROMISING MARKER OF CORONARY HEART DISEASE

The pregnancy-associated plasma protein A (PAPP-A) is a zinc-binding enzyme belonging to the metalloproteinase superfamily, with a high molecular weight (6,7). It was first identified as a circulating protein in the serum of women in advanced stages of gestation (8). Measurement of PAPP-A is useful for screening the foetus for Down syndrome within the first 3 months of pregnancy, as decreased circulating concentrations of this protein are associated with abnormal placental function (8). In addition to placental tissue, PAPP-A is present in a wide variety of reproductive tissues and organs, such as the testicles and endometrium; it is also present in non-reproductive tissues, such as the kidney and colon, but at much lower concentrations than those found during gestation (9). Pregnancy associated plasma protein A is also secreted by osteoblasts, cells of the granular layer of the ovary and vascular smooth muscle cells (10). The circulating form of the protein comprises a heterotetrameric complex formed of two subunits that are 200 kDa and 250 kDa and bound by covalent bonds to two molecules that are 50 kDa and 90 kDa that belong to the proform of eosinophil major basic protein, an endogenous inhibitor of the proteolytic activity of PAPP-A (11). A highly sensitive immunoassay is required to detect PAPP-A protein in normal clinical situations because the concentrations of PAPP-A are 100 times less in the normal population than in gestating women (9). The protein is a specific protease whose substrate is insulin growth factor (IGF), a factor similar to insulin, and one of the IGF binding proteins, IGFBP-4. When IGF is released from its binding to this protein, PAPP-A appears as a growth modulator in local proliferative responses to IGF, such that it influences

the role played by IGF in the pathogenesis of atherosclerosis (12). These actions would give it an important role in the progression of atherosclerosis and the development of restenosis after coronary interventions.

Methods

We searched for published and unpublished studies reported from 2001 to 2009 in PubMed (<http://www.ncbi.nlm.nih.gov>). The electronic search strategy was constructed using the keywords “pregnancy-associated plasma protein A” combined with “coronary artery disease” or “acute coronary syndromes” or “myocardial infarction” or “unstable angina pectoris” in text words or medical subject headings.

We restricted our search to studies of humans and written in English.

We assessed all observational studies published from 2001, when PAPP-A was first considered as a biological marker of unstable atherosclerotic plaques. We included all studies that assessed the association between PAPP-A and acute coronary syndrome (ACS). Studies in which observed patients had stable angina pectoris were excluded.

Results

We found and reviewed 29 references identified through PubMed, 17 of which were excluded after analysing the abstract provided because they did not meet the inclusion criteria.

Five studies assessed the levels of PAPP-A in 306 patients (in total) admitted to the hospital with ACS.

The prognostic role of PAPP-A was investigated in five studies. Cumulatively, these studies included almost 1500 patients. The time of follow-up was from 1 to 12 months. The primary end-point of all studies was cardiovascular death, non-fatal myocardial infarction or revascularisation.

We also included two studies in which the authors attempted to determine the PAPP-A levels after PCI and thrombolytic therapy in ACS in almost 200 patients.

PREGNANCY-ASSOCIATED PLASMA PROTEIN A IN ACUTE CORONARY SYNDROMES

Pregnancy-associated plasma protein A was first considered as a biological marker of unstable atherosclerotic plaques in 2001 after a study by Bayes-Genis et al., who examined the level of expression of PAPP-A in eight culprit unstable coronary plaques and four stable plaques from eight patients who had died suddenly of cardiac causes (13). These authors found that PAPP-A was abundantly expressed in plaque cells and the extracellular matrix of ruptured and eroded unstable plaques, but not in stable plaques (13). Circulating PAPP-A levels were significantly higher in patients with unstable angina or acute myocardial infarction (AMI) than in patients with stable angina and controls ($P < 0.001$). A PAPP-A threshold value of 10 mLU



per litre identified patients who had ACS with a sensitivity of 89.2% and a specificity of 81.3%. PAPP-A levels correlated with free IGF-I and CRP but not with markers of myocardial damage (creatinine kinase MB isoenzyme [CK-MB] and troponin I [TnI]). Khosravi et al. (9) also investigated associations of PAPP-A with myocardial damage in serum samples classified based on serum creatine kinase CK-MB or cardiac troponin-T levels. They found a strong correlation between PAPP-A and Troponin-T ($r = 0.59$, $p < 0.001$) in a subset of troponin-T-positive samples. Opposite results of these studies regarding the correlation of PAPP-A with markers of myocardial damage might be due to the fact that PAPP-A has also been associated with other cardiac markers that could be influenced by their relative release dynamics (i.e., timing and duration). Contrary to the findings of these studies, a study by Domínguez-Rodríguez et al. (14) found no differences between the PAPP-A concentrations in 80 patients with ST-elevation ACS compared to control subjects (26). The authors concluded that PAPP-A is not a valid early marker of AMI. This same study also did not find any correlation between PAPP-A and markers of myocardial necrosis; samples were taken at 6.3 ± 2.8 hours (mean $\pm$ SD) after the onset of symptoms.

In another study with 59 patients presenting with chest pain to the emergency department (ED), elevated serum PAPP-A levels were found to be predictive of a diagnosis of ACS in intermediate- to high-risk patients with chest pain and no definite evidence of ACS (15). Thus, serum PAPP-A may be valuable as an adjunct, minimally invasive marker to improve risk stratification in patients presenting with chest pain.

Schoos et al. assessed 40 patients grouped according to type of ACS (16). In this study, PAPP-A concentrations were measured in serially collected samples. All patients with elevated PAPP-A levels reached the upper reference level within 24 h. There was a significant difference in median peak levels between STEMI (23.2 mIU/L) and low-risk ACS patients (6.35 mIU/L) ($p = 0.004$) and between high-risk (median = 15.3 mIU/L) and low-risk ACS patients ($p = 0.01$). Among high-risk ACS patients, NSTEMI patients had significantly higher peak levels than unstable angina patients ($p = 0.003$).

PROGNOSTIC VALUE OF PAPP-A IN ACUTE CORONARY SYNDROMES

Several studies have demonstrated that PAPP-A may have prognostic value in patients with ACS. Some reports have also examined the risk stratification of patients by PAPP-A alone or in combination with cardiac troponins.

The role of PAPP-A as a prognostic indicator in ACS patients has been assessed in several studies. Laterza et al. (17) tried to determine ability of circulating concentrations of PAPP-A to predict adverse events in patients presenting to the ED with symptoms of ACS ($n = 346$ patients, of whom 33 suffered adverse events) (27). On analysis of the receiver operating characteristic (ROC)

curves, cardiac troponin T (TnT) was found to be a better predictor of events after 30 days than PAPP-A. For a cut-off point of 0.22 mU/L, PAPP-A had a significantly worse specificity than cardiac TnT. Thus, according to this study, PAPP-A was a modest predictor of adverse coronary events 30 days after the index event (17).

In another study, Lund et al. (18) assessed 200 consecutive patients with suspected ACS and undetectable concentrations of TnT for up to 24 hours from admission. Patients with PAPP-A concentrations greater than 2.9 mU/L were at a significantly higher risk of cardiovascular death, a first episode of nonfatal AMI, or need for revascularization after 6 months of follow-up. At a cut-off level of 2.9 mIU/L, elevated PAPP-A was an independent predictor of adverse outcome (adjusted risk ratio [RR], 4.6; 95% confidence interval [95% CI], 1.8 to 11.8; $p = 0.002$). Another independent predictor was admission CRP >2.0 mg/L (RR, 2.6; $p = 0.03$).

Heeschen et al. also showed that determination of PAPP-A provides additional prognostic information in patients with ACS (19). Their study included 547 patients with ACS who underwent coronary angiography before randomization and a heterogeneous group of 626 consecutive patients with acute chest pain lasting less than 12 hours before admission. Blood samples were collected at the time of arrival in the ED (5.1 ± 3.4 h after onset of symptoms and before initiation of treatment), and a second blood sample was drawn 4 h later. PAPP-A and markers of myocardial necrosis (troponin T [TnT]), ischemia (vascular endothelial growth factor [VEGF]), inflammation (high-sensitivity C-reactive protein [hsCRP]), anti-inflammatory activity (interleukin [IL]-10) and platelet activation (soluble CD40 ligand [sCD40L]) were determined. In patients with ACS, elevated PAPP-A levels (above 12.6 mU/L) had a higher incidence of death or nonfatal myocardial infarction, with an odds ratio of 2.74 (95% CI, 1.44 to 5.22; $p = 0.002$) after 72 hours, 2.84 (95% CI, 1.55 to 5.22; $p = 0.001$) after 30 days and 2.44 (95% CI, 1.43 to 4.15; $p = 0.001$) after 6 months. When the analysis was restricted to TnT-negative patients, PAPP-A still identified a subgroup of high-risk patients (odds ratio [OR] 2.72 [95% CI, 1.25 to 5.89]; $p = 0.009$). Prospective validation in patients with chest pain confirmed that PAPP-A levels reliably identified high-risk patients (adjusted OR 2.32 [95% CI 1.32 to 4.26]; $p = 0.008$). An interaction between PAPP-A and interleukin (IL) 10 was shown such that the predictive value of the composite endpoint of death and nonfatal AMI was limited to patients with circulating IL10 concentrations below 3.5 ng/mL. The authors, therefore, concluded that the balance between proinflammatory and anti-inflammatory cytokines determined the course of the disease in these patients, who, in turn, had a higher rate of revascularization procedures. In this study, PAPP-A was also weakly correlated with other biological makers, such as hs-CRP and CD40L, although no correlation was found with TnT (19).



In a small cohort of patients with ST-segment elevation acute MI (n = 62), Lund et al. (20) noticed an early peak of circulating PAPP-A during the 12 h from symptom onset, followed by rapid normalization. Admission PAPP-A levels did not correlate with admission C-reactive protein or cardiac troponin I. The variability of PAPP-A kinetics at 48 h reflects the success of reperfusion. The authors also found that PAPP-A >10mIU/L was a significant predictor of 12-month risk of cardiovascular death or nonfatal MI.

Contrary to the findings of these studies, a recent study by Brugger-Andersen et al. in a patient population consisting of 298 subjects hospitalized with an MI found that a multi-marker approach with NT-proBNP, hsCRP, MMP-9, PAPP-A, MPO, sCD40L and FM rendered no additional prognostic information beyond conventionally used stratification tools in the acute phase (21).

THE EFFECT OF REPERFUSION THERAPY ON PAPP-A LEVELS IN ACUTE MYOCARDIAL INFARCTION

Brugger-Andersen et al. attempted to determine the PAPP-A levels after PCI and thrombolytic therapy with tenecteplase in a group of 38 patients admitted for STEMI (22). They found that the plasma concentrations of PAPP-A increased by a factor of six to eight times ($p < 0.001$) following both reperfusion therapies. Plasma concentrations of PAPP-A increased to a significantly higher level after PCI compared to thrombolytic treatment ($p = 0.002$). This would indicate a greater impact of PCI on the target coronary lesion due to a direct mechanical trauma, resulting in the local release of metalloproteinases into the extracellular space and henceforth systemically, whereas the increase in PAPP-A following thrombolytic therapy is likely derived from both target and systemic plaque vulnerability.

Terkelsen et al. found that PAPP-A was markedly elevated in the earliest hours after the onset of symptoms in patients with STEMI treated with heparin and primary percutaneous coronary intervention (23).

PREGNANCY-ASSOCIATED PLASMA PROTEIN-A AND ACUTE CORONARY SYNDROMES: CAUSE OR CONSEQUENCE?

There are controversial opinions regarding the role of PAPP-A in inflammatory reactions that lead to plaque rupture and clinical instability. Several lines of evidence indicate that PAPP-A is induced in response to and within damaged tissues as a promoter of repair, in virtue of its IGF-1-dependent actions on vasculogenesis, vasodilation, cell preconditioning, cell survival and insulin-sensitivity (24,25). Even mild damage, such as brief ischemia, would activate this pathway (12), thus explaining the higher sensitivity of PAPP-A compared to cardiac troponins as predictors of outcome. In response to necrosis, the broad-ranging fluctuations of PAPP-A justify its correlation with cardiac enzymes (18) and inflam-

matory markers. The remission of rheumatoid arthritis and other inflammatory states during pregnancy (the prototype of increased PAPP-A) denotes PAPP-A as a suppressor, rather than mediator, of inflammation and tissue damage (26).

In contrast, PAPP-A may have a more deleterious role by breaking down the extracellular matrix via its metalloproteinase character.

IGF-1 binds to the type I IGF receptor, which is present on many cell types found in the plaque (12). The outcome of IGF action on different cells, however, relates to other molecules and a complex microenvironment.

In macrophages, IGF promotes excess low-density lipoprotein cholesterol uptake, release of pro-inflammatory cytokines and chemotaxis. This inflammatory environment digests the fibrous cap, leaving the plaque vulnerable to rupture (12). PAPP-A cleaves IGF binding protein 4 and 5 in vitro (27) and may function similarly in vivo to enhance local IGF bioavailability. Recently, it has been demonstrated that PAPP-A expression is significantly enhanced by inflammatory cytokines, such as tumour necrosis factor- in adult human fibroblasts (28). If the same is found to be true in atherosclerotic plaques, increased PAPP-A will further increase levels of local bioactive IGF, thereby causing the plaque to proceed to disruption unless the chain of reactions is interrupted.

IGF-1 has a chemotactic action on vascular endothelial cells and induces endothelial tube-forming activity in vitro (12). The ultimate outcome, however, may be different because of the interactions between various bioactive molecules and cells within the atherosclerotic lesion. A recent study has shown that a long-term low dose of IGF-1 significantly enhances tumour necrosis factor- induced adhesion molecule expression in endothelial cells, suggesting that IGF-1 is an enhancing factor for cytokine-induced endothelial cell inflammation (29).

In vitro IGF-1 plays an important role in migration, cell cycle progression and survival of vascular smooth muscle cells (12). However, there are studies showing that human plaque-derived vascular smooth muscle cells are not responsive to the protective effects of even high levels of IGF-1 in vivo because of reduced IGF-1 receptor expression and increased insulin-like growth factor binding protein synthesis, which can be caused by oxidized low-density lipoprotein, one of the important players in plaque inflammation (30).

Clearly, further studies are needed to prove the exact role of PAPP-A in atherosclerosis and its complications.

CONCLUSION

PAPP-A is a very promising novel biochemical marker for the prediction of first or recurrent coronary events either alone or as a complement to other markers. However, the findings are still preliminary and require further evidence to fully determine the true role of this marker and its application in clinical practice.



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