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THE ROLE OF PREGNANCY-ASSOCIATED PLASMA PROTEIN-A (PAPP-A) IN THE IDENTIFICATION OF CORONARY ARTERY DISEASE ACTIVITY

SUMMARY

Pregnancy-associated plasma protein-A (PAPP-A) is high-molecular-weight metalloproteinase originally identified in the serum of pregnant women. During pregnancy, the concentration of PAPP-A increases in maternal circulation with gestational age. Depressed levels, associated with an abnormal placental function, have formed the basis of the first trimester screening for Down syndrome. The role of PAPP-A in tissue other than placenta has only recently been explored. Higher PAPP-A concentrations have been found in patients with acute coronary syndrome (ACS) when compared to the patients with stable angina and subjects without coronary artery disease. A very recent study indicates that, even in patients with stable coronary heart disease, PAPP-A levels are associated with angiographic plaque complexity and atherosclerotic disease extent.

In addition, elevated PAPP-A concentrations have shown to be associated with adverse cardiac events in ACS patients and in patients with chronic stable coronary artery disease (CSA). Noteworthy, the PAPP-A form that accounts for increase in ACS is non-complexed with the proform of eosinophil major basic protein (proMBP). However, PAPP-A assays applied in clinical studies published thus far detect total PAPP-A. Consequently, the clinical value may be non-optimal when total PAPP-A is measured in patients with coronary artery disease (CAD).

PAPP-A appears to be a very promising biomarker useful in the clinical management of CSA patients. However, more prospective studies with carefully established immunoassays are required to validate its clinical utility.

Key words: **pregnancy-associated plasma protein-A, coronary artery disease**

INTRODUCTION

Pregnancy-associated plasma protein-A (PAPP-A) is a high-molecular-weight, zinc binding matrix metalloproteinase belonging to the metzincin superfamily of metalloproteinases (1,2).

Pregnancy-associated plasma protein-A (PAPP-A) was first identified in the early 1970s in the plasma of pregnant women by Lin et al. (3). It was partially purified together with other pregnancy-associated plasma proteins B, C and D from pregnancy serum (4). The preliminary observation on PAPP-A measurements in late pregnancy has led to optimistic conclusions especially in predicting the occurrence of various obstetric abnormalities; however, the interest in PAPP-A decreased later. A new period of PAPP-A research has appeared after the publication of Brambati et al. (1990), who

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described decreased levels in the pregnancy with fetus affected by Down syndrome.

Another promising area of PAPP-A determination is cardiology. Only recently, it has been shown that PAPP-A is present in eroded and ruptured plaques and that its circulating concentrations are increased in patients with acute coronary syndrome (ACS)(5). However, a very recent study indicates that, even in patients with stable coronary heart disease, PAPP-A levels are associated with angiographic plaque complexity (6) and atherosclerotic disease extent (7).

Structure and synthesis of PAPP-A

Pregnancy-associated plasma protein-A (PAPP-A) gene has been assigned to human chromosome 9q33.1(8). PAPP-A belongs to the metzincin superfamily of metalloproteinases (9). The superfamily presents a diverse group of zinc endopeptidases that includes the astacins, reprolysins, serralysins, and the matrix metalloproteinases (MMPs) (10).

During pregnancy, the vast majority of PAPP-A is synthesized in the placental syncytiotrophoblast (11). In normal pregnancy, the concentration of PAPP-A in maternal circulation increases with gestational age, while the comparatively depressed levels found in association with abnormal placental function has formed the basis for the first trimester screening of fetal Down syndrome (12,13).

Apart from pregnancy, PAPP-A has been found to be secreted by a variety of cultured human cells, such as fibroblasts, osteoblasts, ovarian granulosa cells, endometrial stromal cells and coronary artery vascular smooth muscle cells (14). Furthermore, studies using immunohistochemistry and in situ hybridization identified in vivo PAPP-A produced in vascular plaques (5), and in healing human skin (14).

PAPP-A is secreted as a disulfide bound dimer of 400 kDa (15). In pregnancy serum, the vast majority of PAPP-A (>99%) is covalently bound in a 2:2 complex to the proform of eosinophil major basic protein (pro-MBP) (1,16). It has recently been determined that proMBP functions as a physiological inhibitor of PAPP-A (16), but no mechanism has been established that explains the inhibitory properties of proMBP. Recently, it has been shown that atheromatous plaques contain non-complexed PAPP-A and that elevated concentrations of the same form are found in plasma.

Function of PAPP-A

Knowledge of PAPP-A biological function has been lacking from its discovery in 1974. In the past, several functions have been attributed to PAPP-A such as zinc carrier proteins and barrier against phagocytic-proteolytic defense. Inhibitory effects of leukocyte elastase and lectin-induced lymphoblastogenesis have also been described (4).

Today, it is known that substrates of PAPP-A include insulin-like growth factor-binding proteins (IGFBPs), whose role is in the inhibition of the biological activities of insulin-like growth factors I and II (IGF-I and –II).

Insulin-like growth factors I and II (IGF-I and-II) are single chain polypeptides that share homology with each other and with proinsulin (17). They are regular constituents of human blood plasma. Systemic IGF-I and IGF-II levels are determined mainly by production in the liver. However, many cells of the body synthesize these growth factors (17). The IGFs have a broad range of physiological actions starting with early embryonic development and extending throughout life. Metabolic functions, particularly glucose metabolism, constitute an important aspect of IGF-I and -II activities (18). The IGFs also induce differentiated functions of cells stimulating amino acid uptake and protein synthesis, and promoting migration (18). Another prominent aspect of IGF-I is the regulation of cell cycle progression and mitogenesis (19,20) IGFs may also function as survival factors by decreasing apoptosis in various cells (21).

Insulin-like growth factors (IGFs) and their regulatory proteins, secreted by cells of the cardiovascular system, are growth promoters for arterial cells and mediators of cardiovascular diseases (22). Dysregulated actions of these factors contribute to coronary atherosclerosis.

Pregnancy-associated plasma protein-A (PAPP-A), as a IGFBP proteases, IGFBPs and IGF appear to function together in several systems, particularly the reproductive system and the cardiovascular system (10).

The dynamic balance (IGFs, IGFBPs, and IGFBP proteases) constitutes the IGF axis and ultimately determines the extent of IGF-dependent cellular effects. Dysregulated actions of this axis influence coronary atherosclerosis through effects on vascular smooth muscle cell growth, migration and extracellular matrix synthesis in the atherosclerotic plaque (18).

Insulin-like growth factor (IGF-1) binds to the type I IGF receptor, which is present on many cell types, including vascular smooth muscle cells, endothelial cells, and macrophages, which are often found in the fibrous cap and around the lipid core of the atherosclerotic plaque (15,18). In vascular smooth muscle cells, IGFs stimulates migration and proliferation. Insulin-like growth factor has a

chemotactic action on vascular endothelial cells (15). In macrophages, IGF promotes excess LDL-cholesterol uptake; release of proinflammatory cytokines, e.g., tumor necrosis factor and chemotaxis. This inflammatory environment contains many matrix-degrading metalloproteinases and is able to digest the fibrous cap that overlies the lipid-rich core, leaving the plaque vulnerable to rupture (15,18). More recently, it has been demonstrated that PAPP-A production is significantly enhanced by inflammatory cytokines, such as tumor necrosis factor in adult human fibroblasts (23). If this is also true in atherosclerotic plaques, then increased PAPP-A will further increase concentrations of local bioactive IGF, which in turn leads to formation of more foam cells and release of more proinflammatory cytokines, progressing to disruption of the plaque unless the chain of reactions is interrupted (15). These findings suggest that PAPP-A plays an important pathophysiological role in destabilization of the atherosclerotic plaque.

Pregnancy-associated plasma protein- A was first considered as a biological marker of unstable atherosclerotic plaques after a study by Bayes-Genis et al., who investigated culprit unstable coronary plaques and stable plaques from eight patients who had died suddenly of cardiac causes (5). These authors found high levels of PAPP-A in the cells and the extracellular matrix of the plaques that showed rupture or erosion compared to stable plaques (5). Given then that this is a marker of plaque instability, its usefulness in the control and stratification of patients who visit the emergency room with chest pain has also been assessed. Several studies have shown that circulating concentrations of PAPP-A are higher in patients with ACS than in those with stable coronary artery disease and control subjects (5). Likewise, PAPP-A concentrations were correlated with free IGF-I and CRP, but not with markers of myocardial damage (creatinine kinase MB isoenzyme [CK-MB] and troponin I [TnI]). This finding differs from that obtained in the study by Khosravi et al., who reported a correlation between concentrations of PAPP-A and troponin (24). These authors also found significantly higher concentrations of PAPP-A in patients with ACS than in those who were suffering from chronic coronary artery disease ($P<0.001$) and in control subjects ($P<0.001$). In these patients with ACS, the pattern of release of PAPP-A is very variable - significant elevations have been reported as long as 30 hours after the index event (25). The kinetics of PAPP-A release and the corresponding protocols for obtaining optimum samples have yet to be fully established. Contrary to the findings of these studies, a recent study by Domínguez-Rodríguez et al. found no differences between the PAPP-A concentrations of 80 patients with ST-elevation ACS compared to control subjects (26). The authors concluded that PAPP-A is not a valid early marker of acute myocardial infarction (AMI). This same study also did not find any correlation between PAPP-A and markers of myocardial necrosis. The samples were taken a mean±SD of 6.3±2.8 hours after the onset of symptoms.

To investigate the prognostic value of determining PAPP-A in patients with coronary artery disease, Laterza et al. studied patients with clinical signs and symptoms of ACS (n=346 patients, of whom 33 suffered adverse events) (27). On analysis of the receiver operating characteristics (ROC) curves, cardiac troponin T (TnT) was found to be a better predictor of events after 30 days than PAPP-A. For a cutoff 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 (27).

In another study with 200 consecutive patients with suspected ACS, patients with undetectable concentrations of TnT and 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. The predictive value of PAPP-A remained after adjusting for age, sex, smoking habit, hypertension, prior AMI (RR=4.6; 95% CI, 1.8-11.8; $P=0.002$) (28).

In a study published recently, Heeschen et al. have showed that determination of PAPP-A provides additional prognostic information in patients with ACS (29). In their study, which included 547 patients with ACS, the authors found that patients with PAPP-A concentrations in the fourth and fifth quintiles, that is with PAPP-A above 12.6 mU/L, had a higher incidence of death or nonfatal AMI, with an odds ratio of 2.74 (95% CI, 1.44-5.22; $P=0.002$) after 72 hours, 2.84 (95% CI, 1.55-5.22; $P=0.001$) after 30 days, and 2.44 (95% CI, 1.43-4.15; $P=0.001$) after 6 months. This predictive value of the PAPP-A concentrations was maintained in patients who did not present increased TnT. 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 weekly correlated with other biological

makers, such as hs-CRP and CD40L, although no correlation was found with TnT.

The possible role of PAPP-A was also investigated in the group of patients with stable coronary disease. Cosin-Sales et al. reported evidence that the patients with complex coronary lesions according to coronary angiography had significantly higher circulating concentrations of PAPP-A (5.89 [1.64] mU/L) compared to patients free of such lesions (5.07 [1.39] mU/L; $P<0.001$) (6). In the same study, the authors investigated the hypothesis that the PAPP-A/pro-MBP ratio could be an indicator of proteolytic activity of PAPP-A and that the ratio could be used as a marker of vulnerable atherosclerotic plaques in patients with chronic stable angina. The proform of eosinophil major basic protein is the endogenous inhibitor of this proteolytic activity of PAPP-A. Cosin-Sales et al. (6) reported that patients with complex coronary lesions had a significantly higher PAPP-A/pro-MBP ratio (3.13 [1.17] mU/L vs 2.66 [0.82] mU/L; $P<0.001$). In the multivariate analysis, the PAPP-A/pro-MBP ratio was an independent predictor of the number of complex lesions, as was male sex and extent of coronary artery disease. The same authors, in their other study comprising 643 patients have showed that PAPP-A levels were higher in patients with multi-vessel disease than those with single-vessel disease and patients without obstructive CAD (7). Extending these findings, it has been shown that in patients with chronic stable CAD, increased plasma PAPP-A concentration is a predictor of all-cause mortality (30,31). In these studies, the prognostic value of PAPP-A was independent of conventional coronary artery atherosclerosis risk factors, extent of CAD and ejection fraction. These findings are of interest as PAPP-A appears to contribute information which is independent and complementary to that afforded by conventional risk markers and markers of inflammation.

Elevated concentrations of PAPP-A were also associated with the presence of atherosclerotic carotid lesions, which were hyperechoic or isoechoic (type V or greater according to the American Heart Association classification) in ultrasonography of the carotid arteries of asymptomatic subjects with hyperlipidemia and at a high cardiovascular risk (32). The patients with such lesions had significantly higher plasma levels than those with hypoechoic lesions ($P<0.05$) and those with normal lipid levels ($P<0.05$) (33). In these patients, determination of PAPP-A was related to CRP levels.

The possible relationship of PAPP-A with other cardiovascular risk factors, such as hypercholesterolemia have been analyzed but with contradictory results (33,34). Stulc et al. studied 27 patients with untreated hypercholesterolemia and no clinical manifestations of atherosclerosis (34). The authors reported significantly higher concentrations of PAPP-A in patients than in control subjects ($P<0.018$), indicating a potential role of PAPP-A as a marker of preclinical atherosclerosis, although more studies would be needed to confirm the value of PAPP-A as such a marker, as well as its value as a marker of plaque instability. However, in a study of 64 hyperlipidemic subjects performed by Beaudeux et al., no differences were found between subjects with hyperlipidemia and control subjects (33). Similarly, no correlation was reported between PAPP-A and cholesterol concentrations (or between PAPP-A and CRP, high density lipoproteins [HDL], and triglycerides) and PAPP-A concentrations remained unchanged after 10 weeks of treatment with 20 mg of atorvastatin, even though total cholesterol, LDL-C, and CRP decreased sharply. The fact that statin treatment did not affect PAPP-A levels, unlike other inflammatory markers, may be partly explained by the role of PAPP-A in the proliferative responses of the plaques rather than plaque inflammation (34). In short, the available evidence seems to suggest that measuring plasma concentrations of PAPP-A could play a role as a marker of unstable atherosclerotic plaques and have prognostic value in patients with chronic stable CAD and ACS. Such measurements could also add information to that provided by markers of myocardial damage, particularly in patients where such markers are not elevated.

PAPP-A assays

Although PAPP-A shows some promise as a marker for cardiovascular disease progression, its measurement does present some problems using existing assays. In the circulation, the PAPPA molecule normally exists as a complex with its endogenous inhibitor proMBP, as mentioned previously. This complex is found at low levels in normal individuals and high levels during pregnancy (35).

Recently, Qin *et al*. have shown that atheromatous plaques contain non-complexed PAPP-A and that elevated concentrations of the same form are found in plasma (15,36). Importantly, they also showed that antibodies raised against the complexed form do not interact with the non-complexed form.

Bayes-Genis *et al*. were the first to show that unstable plaques contained PAPP-A and that patients with CAD had elevated serum concentration of PAPP-A (5). However, their assay, which is similar to that used by Elesber et al. and Cosin-Sales et al. was

based on antibodies that may or may not have been raised against the non-complexed form of PAPP-A, as the authors did not specify this matter (6,7,30). This assay has never been made available commercially. In addition, the standard material against which the assay was calibrated was WHO reference standard 78/610 which was derived from serum collected from pregnant subjects. How appropriate this material is for use in assays to determine PAPP-A in plasma from patients with CAD is a contentious issue.

Although sensitive commercial assays, based on a variety of detection antibodies, are now available to measure PAPP-A, they also have been calibrated against material on the basis of complexed PAPP-A found in pregnant women. Though the available data suggest that these assays are capable of associating measured concentrations of PAPPA with cardiovascular events and extent and complexity of coronary atherosclerosis, it would be better if the assays used to investigate any relationship were calibrated against the analyte of interest (35).

CONCLUSION

The evidence available on pregnancy-associated plasma protein-A (PAPP-A) is promising and this biomarker of activity may become useful either alone or as a complement to other markers, such as C-reactive protein (CRP), in predicting cardiovascular risk. However, the findings are still preliminary and require further evidence and more studies to fully determine the true role of this marker and its application in clinical practice and to standardize the measurements and corresponding protocols to determine the plasma concentrations of this marker.

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ULOGA PAPP-A U IDENTIFIKACIJI AKTIVNOSTI KORONARNE ARTERIJSKE BOLESTI

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SAŽETAK

Pregnancy-associated plasma protein (PAPP-A) je visokomolekularna matriks metaloproteinaza prvobitno izolovana u serumu gravidnih žena. U toku trudnoće, koncentracija PAPP-A u krvi majke raste, dok su sniženi nivoi dovedeni u vezu sa poremećenom placentarnom funkcijom koja se manifestuje u ranoj dijagnozi Down-ovog sindroma. Ispitivanje uloge PAPP-A u drugim tkivima organizma počelo je nedavno. Povišene vrednosti PAPP-A nađene su kod bolesnika sa akutnim koronarnim sindromom (ACS) u odnosu na bolesnike sa stabilnom anginom pektoris i zdravu populaciju. Najnovije studije su pokazale da kod bolesnika sa stabilnom koronarnom bolešću nivo PAPP-A korelira sa kompleksnošću aterosklerotskih lezija, kao i da su koncentracije ove metaloproteinaze veće kod višesudovne bolesti.

Povišeni nivoi PAPP-A dovedeni su u vezu sa lošom prognozom kod bolesnika sa akutnim koronarnim sindromom i kod bolesnika sa stabilnom koronarnom bolešću. Važno je napomenuti da PAPP-A koji se nalazi u cirkulaciji bolesnika sa koronarnom bolešću cirkuliše u slobodnoj formi, dok je kod trudnica prisutan kompleks PAPP-A i eozinofilne proforme major basic proteina (proMBP). To dovodi u pitanje adekvatnost korišćenih podloga koje su sintetisane za detekciju komleksne forme PAPP-A.

PAPP-A predstavlja koristan biomarker u kliničkom sagledavanju bolesnika sa koronarnom bolešću. Ipak, neophodne su nove prospektivne studije primenom adekvatnih podloga za detekciju PAPP-A da bi se procenila prava uloga ove metaloproteinaze u kliničkoj praksi.

Ključne reči: **PAPP-A, koronarna bolest**