Review

Pregnancy-associated plasma protein A: spotlight on kidney diseases

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Abstract

Pregnancy-associated plasma protein A (PAPP-A) is a biomarker routinely used in screening for Down syndrome in the first trimester of pregnancy. It is also present in very small amounts in men and non-pregnant women. PAPP-A is a key regulator of local insulin-like growth factor (IGF) bioavailability – IGFs are essential for normal body size during fetal development, but they are associated with aging and age-related diseases. Measurement of circulating PAPP-A can provide valuable information not only in pregnant women (chromosomal anomalies and adverse pregnancy outcomes) but also in patients with coronary artery disease (contribution to diagnosis, prognostic value) and in patients with kidney diseases. PAPP-A is associated with renal function and proteinuria, is increased mainly in dialysis patients and decreases after kidney transplantation. It is an independent mortality predictor of hemodialysis patients and indicator of adverse outcome of transplanted patients. PAPP-A levels can be influenced by various chemicals and drugs, among them mainly heparin. Various assays for PAPP-A exist and the type of assay used in a study should be considered. This article reviews the data summarizing basic information about PAPP-A with a particular focus on the significance of PAPP-A in renal diseases.

Keywords: dialysis; kidney; polymorphism; predictive value; pregnancy-associated plasma protein A; transplantation.

Introduction

Pregnancy-associated plasma protein A (PAPP-A) is a biomarker routinely used in screening for Down syndrome in the first trimester of pregnancy. Despite its name “pregnancy protein” it is also present in very small amounts in non-pregnant individuals, both men and women and is implicated in various processes, such as wound healing, bone remodeling or atherosclerosis. Measurement of circulating PAPP-A can provide valuable information not only in pregnant women but also in patients with coronary artery disease and in patients with kidney diseases.

In this review we would like to summarize basic information about PAPP-A and focus on the significance of PAPP-A in renal diseases – what was demonstrated in experimental, genetic, laboratory, clinical and pharmacological studies.

History of PAPP-A in laboratory medicine

PAPP-A was originally isolated in 1974 as one of four placental proteins circulating in high concentrations in pregnant women (1). In 1990 it was shown that low maternal serum level of PAPP-A in the first trimester of pregnancy is characteristic for Down syndrome fetus development (2), and measurement of PAPP-A was introduced in the first trimester screening of chromosomal anomalies (3). There is increasing evidence that low levels of PAPP-A in the first trimester are associated with adverse outcomes, such as preterm delivery, intrauterine growth retardation, preeclampsia, and stillbirth (4). In the third trimester in preeclamptic pregnancies, PAPP-A is increased (5).

In 2001, PAPP-A was found in eroded and ruptured atherosclerotic plaques and its serum levels were increased in patients with acute coronary syndromes (6). Many studies regarding the usefulness of PAPP-A screening in cardiology were performed. PAPP-A was demonstrated as a marker of the presence and extent of atherosclerosis in coronary and peripheral arterial diseases, a marker of outcome in stable atherosclerotic disease and in some studies as a marker of worst prognosis in acute coronary syndrome and as a marker that might help in the diagnosis of acute coronary syndrome [reviewed in (7)]. Controversy exists due to different assays used in the studies.

In 2003, we first described elevation of PAPP-A in patients with end-stage renal disease treated with hemodialysis (8), and subsequently its relationship to renal function (9) and its possible prognostic role in long-term hemodialysis patients.
Elevation of PAPP-A measured by a different method with lower reference range was also confirmed by Coskun et al. (11).

PAPP-A has been studied in a variety of diseases, e.g., in diabetes mellitus, allergy and obesity. In diabetic patients, no difference in PAPP-A levels in DM1 or DM2 and healthy subjects was found (12) and another group did not find its usefulness as a biomarker of carotid atherosclerosis in type 2 diabetics (13). Conversely, PAPP-A was associated with increased mortality in type 1 diabetic patients with nephropathy but only in unadjusted analysis; after adjustment for traditional risk factors the prognostic value of PAPP-A was no longer significant (14). PAPP-A was significantly elevated in allergic rhinitis (15) and in asthma and correlated with asthma severity (16). In children there was no difference between obese and lean subjects but a correlation with other cardiovascular risk factors was found (17).

**Biology of PAPP-A: gene structure and function**

The gene for PAPP-A in humans is located on chromosome 9q33.1 (18), spans over 200 kb of DNA, and contains 22 exons with a length from 72 to 1063 nucleotides separated by 21 introns of various length (19). PAPP-A is synthesized as a 1627-residue precursor preproprotein with a 22-residue putative signal peptide and a propeptide of 58 residues, so that the mature protein then contains 1547 amino acids. PreproPAPP-A mRNA has an unusually long 5′ untranslated region that contains several ORF (20). The PAPP-A amino acid sequence is, to a high extent, identical with other mammals which suggests its essential function. Additionally, PAPP-A was also found in non-mammalian vertebrates but not in invertebrates (21).

The PAPP-A protein (PAPP-A monomer) containing 1547 amino acids has pI 5.4 and molecular weight 200 kDa. It is composed of five domains: the N-terminal laminin like domain, the metzincin proteolytic domain which is responsible for insulin-like growth factor binding proteins (IGFBPs) cleavage, a central domain of unknown identity, a domain defined by five complement control protein modules which is responsible for binding to the cell surface and a C-terminal domain (21). PAPP-A exists as a homodimer of 400 kDa which is proteolytically active and as a proteolytically inactive PAPP-A/pro major basic protein (MBP) heterotetrameric complex of 500 kDa (21). The complexed PAPP-A is the major form of PAPP-A in pregnancy (22) while the free (uncomplexed) form is the only relevant form in acute coronary syndromes (23).

PAPP-A is expressed by various cell types – fibroblasts, vascular smooth muscle cells, osteoblasts, ovarian granulose cells, trophoblasts cells, and to a lesser extent by endothelial cells. It is not expressed by macrophages (21). PAPP-A is secreted and then binds to cell surfaces in an autocrine/paracrine manner (24, 25).

PAPP-A (pappalyasin-1, E.C. 3.4.24.79) is a zinc binding protease which together with PAPP-A2 (pappalyasin-2) and ulilysin belongs to pappalyasins, one of five subfamilies of the metzincin superfamily of metalloproteinases. PAPP-A2 shares 45% homology with PAPP-A and unlike PAPP-A it is unable to bind to cells. Ulilysin was found in archebacteria *Methanosarcina acetitovorans* (26). PAPP-A is responsible for proteolytic cleavage of IGFs, mainly IGFBP-4 but also -2 and -5 and so acts as a positive regulator of IGF availability (27–29). PAPP-A is a key regulator of IGF-II bioavailability during early embryogenesis and plays a similar role regulating IGF-I bioavailability postnatally (21). PAPP-A like other metzincins has the ability to cleave itself resulting in fragments of 150 kDa and 50 kDa (30).

PAPP-A is present in healthy individuals in very low concentration (6, 8). During normal pregnancy it rises linearly and after labor it disappears from circulation with a half-life of 3–4 days (31). In acute coronary syndromes it is increased early after the onset of symptoms (first ca 7 h) (32).

**Experimental studies**

PAPP-A is a key regulator of local IGF bioavailability. IGFs are essential for normal body size during fetal development, however, IGFs are associated with aging and age-related diseases. That is why loss of PAPP-A or inhibition of PAPP-A activity should have negative effects early in life and beneficial effects later in life (33).

PAPP-A knockout mice are smaller in body size but have significantly increased life span compared with wild-type littermates. Incidence of neoplastic disease was not significantly different in wild-type and PAPP-A knockout mice; however, it did occur in older aged PAPP-A knockout mice compared to wild-type mice. Additionally, PAPP-A knockout mice were less likely to show degenerative changes of aging. Nephropathy was more evident and more severe in wild-type than in PAPP-A knockout mice. The kidney, an organ with the highest PAPP-A expression levels in wild-type mice, had the most marked changes in gene expression in PAPP-A knockout mice (34). Swindel et al. (35) demonstrated higher expression of IGFBPs-1 and 2, decreased expression of IGFBPs-3 and 5 and no change of IGFBP-4 expression in PAPP-A knockout mice compared to wild-type mice.

In contrast, transgenic mice with over expression of PAPP-A in arterial smooth muscle show accelerated atherosclerotic lesion development (36).

**Genetic studies**

In the database of polymorphisms of the National Center for Biotechnology Information the following polymorphisms are registered (July 27, 2011): 44 polymorphisms in exon sequences, 37 polymorphisms in non-translated regions and more than 2000 polymorphisms in intron sequences. In exons, 13 synonymous polymorphisms (silent mutations), 26 non-synonymous polymorphisms and two deletions are found (Table 1).

Only three papers studying PAPP-A polymorphisms have been published to date. The first found a relationship between...
Table 1  Single nucleotide polymorphisms in exon parts of the PAPP-A gene.

<table>
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<th>Exon</th>
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<th>Non-synonymous</th>
<th>Deletion</th>
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Table 2  Summarization of main findings regarding PAPP-A in patients with kidney disease.

Chronic kidney disease not dialyzed
• Association with renal function and proteinuria
Peritoneal dialysis
• Increased PAPP-A compared to controls, lower levels than in hemodialysis
• PAPP-A detectable in spent dialysate – correlation with protein losses and with marker of peritoneal damage CA-125
Hemodialysis
• Increased PAPP-A compared to controls, higher levels than in peritoneal dialysis
• Correlation with related molecules (IGF-1, IGFBP-4, MMPs and cardiac markers)
• No difference between PAPP-A behavior during hemodialysis and hemodiafiltration
• Similar behavior of PAPP-A during hemodialysis with diacetatecellulosic, polyamid and polysulfon membranes
• Independent mortality predictor of overall mortality and mortality due to infection
Transplantation
• Decrease of PAPP-A after kidney transplantation
• Correlation with graft function
• Correlation with inflammatory markers
• Correlation with histological changes in 3-months protocol biopsy
• Pre-transplant serum concentrations are a predictor of post-transplant cardiovascular events, chronic allograft nephropathy and delayed graft function
searching for three polymorphisms Arg654Lys, Ala678Pro and Thr686Ala in exon 5, and two polymorphisms Phe802Leu, and Ser827Ser/Leu in exon 7, and for new mutations in exon 5 and 7 of the PAPP-A gene in a group of over 200 subjects; however, we did not find any divergence from wild-type form for these polymorphisms in any of the studied subjects, which lead us to the hypothesis that these polymorphisms are not associated with the Caucasian population (39).

No study regarding PAPP-A gene polymorphisms is available in patients with kidney diseases.

PAPP-A assays

Several PAPP-A assays, in house or commercial, with different specificities exist and are used for measurement of PAPP-A. That is why reference ranges and values in studied groups in various studies sometimes differ. PAPP-A assays usually measure total PAPP-A (i.e., PAPP-A/proMBP and free PAPP-A). Concentration of free PAPP-A is the difference between total PAPP-A and complexed PAPP-A, i.e., difference between two assays. Direct free PAPP-A determination is to date not available.

As already mentioned, PAPP-A in pregnancy is predominantly complexed with proMBP. This complex is also present at very low concentration in non-pregnant individuals. In hemodialysis patients, both total and free PAPP-A concentrations is increased (40). In patients with acute coronary syndromes, the PAPP-A increase is given by the increase of free (uncomplexed) PAPP-A and this increase might not always be detected by classical tests used in pregnancy (23, 41, 42). Additionally, PAPP-A can be degraded into smaller fragments of 150 kDa and 50 kDa and it is questionable whether these fragments are also detected by the assays and whether they are relevant for diagnostics. Without a doubt, standardization of the assay would be essential.

Studies in nephrology unlike cardiology are relatively rare. In our studies as well as in the study of Etter et al. (43) PAPP-A was measured by TRACE (Time Resolved Amplified Cryptate Emission) using the KRYPTOR analyzer (BRAHMS GmbH, Henningsdorf, Germany, www.brahms.de). The assay contains two anti-PAPP-A monoclonal antibodies. The manufacturer declares a detection limit of 4 mIU/L, median normal values of 10 mIU/L and concentration of 95% samples of healthy men and women below 14 mIU/L. In our study, PAPP-A concentration in controls was 9.4±2.5 mIU/L (median 9.4 mIU/L, interquartile range IQR 7.3–11.4 mIU/L, 66 subjects) and in hemodialysis patients 27.6±15.5 mIU/L (median 23.4 mIU/L, IQR 18.5–30.8 mIU/L, 261 subjects, basal values – predialysis) (44). In the study of Etter et al. (43), PAPP-A levels in 170 hemodialysis patients were 21 (15–26) mIU/L (median, IQR). Conversely, Lauzurica et al. (45) and Coskun et al. (11) used the ultrasensitive PAPP-A assay by Diagnostic Systems Laboratories (Webster, TX, USA). Coskun et al. measured PAPP-A concentration 3.5 (3.0–5.0) mIU/L in control subjects and 4.7 (3.8–6.5) mIU/L in hemodialysis patients (medians and IQR) (11) while Lauzurica describes lower levels – median 0.96 mIU/L and rank 0.16–3.08 mIU/L in healthy controls and median 2 mIU/L and rank 0.19–12.86 mIU/L in dialysis patients before transplantation (45). Tertti et al. measured total PAPP-A and complexed PAPP-A on an Aio Immunoanalyzer (Innotrac Diagnostics). Total PAPP-A concentration in hemodialysis patients was 9.0 (6.9–11.9) mIU/L and concentration of free PAPP-A was 5.2 (4.2–7.0) mIU/L (median and IQR) (40).

Another point that should be addressed is timing of PAPP-A collection since it can be influenced by previous application of heparin (see below) (40). Of note, in vitro addition of heparin to blood does not influence PAPP-A concentration.

Clinical and laboratory studies in patients with kidney diseases

In 2003, we first described elevation of PAPP-A in patients with end-stage renal disease treated with hemodialysis (8). PAPP-A levels are three-fold higher than in healthy controls, however, 100–1000-fold lower than in the first trimester of pregnancy. Elevation of PAPP-A in hemodialysis patients measured by a different method giving lower values was confirmed Coskun et al. (11).

PAPP-A is associated with renal function (9) as well as with proteinuria and negatively with albumin (46). PAPP-A is significantly elevated mainly in patients with end-stage renal disease with lower levels in patients treated with peritoneal dialysis than in patients treated with hemodialysis (9). PAPP-A is detectable also in spent peritoneal dialysate but these concentrations are not related to serum levels. However, PAPP-A in dialysate significantly correlates with protein losses to the dialysate (r=0.66, p<0.05) and with CA 125 as a marker of peritoneal damage (r=0.56, p<0.05) (our unpublished observation). In hemodialysis patients PAPP-A correlates significantly with another pregnancy protein, placent growth factor (PIGF), matrix metalloproteinases MMP-2 and 9, molecules linked to its action IGF-1 and IGFBP-4 and cardiac markers troponin (cTnI) and brain natriuretic peptide (BNP) and creatinine. We did not find an association with albumin, cholesterol, CRP, orosomucoid, and retinol (44). Concerning its changes during dialysis, PAPP-A significantly increases at the beginning of the procedure – hemodialysis or hemofiltration – without a difference between these two procedures, probably due to heparin application and then decreases until the end of the procedure (47). Similar behavior of PAPP-A during hemodialysis with diacetatecellulosic, polyanid (48) and polysulfon membranes was observed (49).

PAPP-A decreases after kidney transplantation, and correlates with graft function and with histological changes in 3-month protocol biopsy (intragraft interstitial inflammation and intima thickening) (50). However, PAPP-A is higher in transplanted patients than in patients with chronic kidney disease with the same glomerular filtration rate (50). It is significantly correlated with inflammatory markers C-reactive protein, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (45).

In 2004, we described in our preliminary study of 40 hemodialysis patients higher PAPP-A levels in patients who died...
during the 20-months follow-up compared to survivors suggesting a possible prognostic role of PAPP-A (10). Our hypothesis was confirmed in our definitive study in 261 long-term hemodialysis patients who were followed for 5 years – PAPP-A was an independent predictor of overall mortality and mortality due to infection in hemodialysis patients (44). Similarly, PAPP-A was shown as an independent short-time predictor of mortality in a smaller study (170 patients) (43). Additionally, several studies dedicated to PAPP-A in renal transplant recipients – its pre-transplant serum concentration serves also as a predictor of post-transplant cardiovascular events and chronic allograft nephropathy (45) and could be a risk factor of delayed graft function (51). Similarly, as in patients with acute coronary syndrome, coronary artery disease and peripheral artery disease where PAPP-A was identified as an independent marker of cardiovascular events and death (7), elevated PAPP-A in hemodialysis patients could be a surrogate marker reflecting systemic atherosclerosis and adverse outcome (Table 2).

**Pharmacological influence of PAPP-A expression and circulating PAPP-A levels**

PAPP-A expression is stimulated by TNF-α and interleukin 1 beta (IL1-β) (52–54) and this cytokine induced expression can be inhibited by antioxidants N-acetyl cysteine (53) or polyphenol resveratrol (54). Resveratrol is found in the skin of grapes and in red wine which might contribute to the explanation of the French paradox of beneficial effect of consumption of red wine on reduced cardiovascular risk. Antioxidant vitamin E (400 mg daily for 5 weeks) in long-term hemodialysis patients had no effect on PAPP-A levels (55).

The effect of statins on PAPP-A levels was tested in small clinical studies. Atorvastatin in high-dose (80 mg) significantly decreased PAPP-A after 1-month treatment while a low dose of atorvastatin did not have this effect (56). Another study did not demonstrate any effect of 20 mg atorvastatin daily on PAPP-A levels (57).

PAPP-A levels are significantly increased by heparin administration (unfractionated heparin as well as low molecular weight heparin enoxaparin) but are not influenced by another anticoagulant, bivalirudin (40, 58). Total PAPP-A increased up to 25-fold within 5 min after heparin administration and the increase was given by free PAPP-A. Free PAPP-A was then cleared rapidly, 85% in the first rapid phase (half-life 13.1 min) and the remaining 15% in the second slower phase (half-life 96.6 min) (58). Repeated heparin bolus induced a new PAPP-A release. Subcutaneous low molecular weight heparin led to lower and slower free PAPP-A elevation. An increase of total PAPP-A at the beginning of hemodialysis (PAPP-A measured 15 min after start of dialysis and after heparin application) was also observed by our group (47, 48). We discussed the possible effects of heparin (47) and its role in PAPP-A redistribution as binding of PAPP-A to heparin-Sepharose was used for PAPP-A purification from pregnant plasma in 1983 (59). As heparin is widely used in patients with acute coronary syndromes and hemodialysis patients and expert evaluation of heparin administration in patients was published only in 2009 (40), this might have influenced the results of some previous studies and explain some discrepancies in study results. In our studies, blood for basal PAPP-A was collected before heparin administration and patients with permanent catheters were excluded to avoid possible influence on the results.

Sodium ferric gluconate is another drug increasing PAPP-A levels. We have observed a two-fold increase in PAPP-A 1 h after administration of 62.5 mg sodium ferric gluconate which is indispensable for proper function of erythropoietin in hemodialysis patients, and its subsequent decrease (49) (Table 3).

**Summary**

In summary, PAPP-A is a protein with many functions within as well as outside pregnancy. Measurement of circulating PAPP-A can bring valuable information in pregnant women and also in patients with coronary artery disease and in patients with kidney diseases. PAPP-A is associated with renal function and proteinuria, is increased mainly in dialysis patients and decreases after kidney transplantation. It is an independent mortality predictor of hemodialysis patients and indicator of adverse outcome of transplanted patients. However, various assays for PAPP-A exist and the type of assay used should be considered. Further studies with higher numbers of patients and standardization of PAPP-A assay are required to show the usefulness of PAPP-A measurement and enable its possible introduction into routine clinical practice in other indications than first trimester pregnancy screening.

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References


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Prof. Vladimír Tesář, MD, PhD, MBA, FASN, FERA, was born May 5, 1957 and graduated in 1982 from the 1st Faculty of Medicine, Charles University, Prague. He is Professor of Medicine (since 1999) and the Head of Department of Nephrology, 1st Faculty of Medicine, Charles University (since 2003). His main areas of interest are glomerular disease (ANCA-vasculitis, lupus nephritis, membranous and IgA nephropathy), cardiovascular complications of chronic kidney disease and hereditary diseases of the kidney. Prof. Tesář is an author and co-author of more than 260 peer reviewed publications in leading journals and one of the main authors of two monographs. He is a member of many scientific societies (e.g., Fellow of the American Society of Nephrology since 2005) and editorial boards (e.g., *Folia Biologica, Kidney and Blood Pressure Research, Blood Purification*).

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