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Serum pregnancy-associated plasma protein A correlates with inflammation and malnutrition in patients treated with maintenance hemodialysis

Małgorzata Mazur-Laskowska[1], Agnieszka Gala-Błądzińska[2], Paulina Zegartowska[3], Paulina Dumnicka[4], Anna Ząbek-Adamska[1], Maria Kapusta[5], Aleksandra Maleszka[1], Barbara Maziarz[1], Marek Kuźniewski[6], Beata Kuśnierz-Cabala[5]

[1]Diagnostic Department of University Hospital in Kraków, Poland
[2]St' Queen Jadwiga Clinical District Hospital No 2 in Rzeszów, Poland
[3]Faculty of Medicine, Nutrition Direction, Jagiellonian University Medical College, Kraków, Poland
[4]Department of Medical Diagnostics, Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland
[5]Department of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian University Medical College, Kraków, Poland
[6]Department of Nephrology, Jagiellonian University Medical College, Kraków, Poland

Corresponding author: Beata Kuśnierz-Cabala, PhD, Department of Diagnostics, Chair of Clinical Biochemistry, Jagiellonian University Medical College
ul. Kopernika 15A, 31-501 Kraków, Poland; Phone/fax: +48 12 424 83 65; E-mail: mbkusnie@cyf-kr.edu.pl

Abstract: Advanced chronic kidney disease (CKD) leads to complications such as anemia, electrolyte abnormalities, bone and mineral disorder, and malnutrition-inflammation-atherosclerosis (MIA) syndrome, that result in high cardiovascular mortality. One of the biomarkers associated with inflammation and cardiovascular events is pregnancy-associated plasma protein A (PAPP-A). The aim of the study was to measure serum PAPP-A in hemodialyzed CKD patients, and to investigate its correlations with the laboratory markers of the complications. We enrolled 78 consecutive stable adult CKD patients treated with maintenance hemodialysis for median period of 60 months. PAPP-A concentrations were measured with by *electrochemiluminescence* immunoassay. Average serum PAPP-A in hemodialyzed patients was almost two times higher than the upper reference limit. It positively correlated with N-terminal pro-brain natriuretic peptide (NT-proBNP), serum sodium, and the markers of inflammation and malnutrition. In conclusion, serum PAPP-A seems a useful biomarker associated with cardiovascular dysfunction, inflammatory state and malnutrition in hemodialysis patients.

Key words: hemodialysis, cardiovascular diseases, pregnancy-associated plasma protein A, malnutrition.

Introduction

PAPP-A (pregnancy-associated plasma protein A), known also as pappalysin, was first described by Lin in 1974 as one of four serum proteins produced by the placenta [1]. Since late 1990's, the measurements of serum PAPP-A concentrations together with free βhCG in the first trimester of pregnancy have been used in the prenatal screening for *fetal chromosomal abnormalities* (Down syndrome, Edwards syndrome) [2]. Intensive research on PAPP-A has lead to the discovery of its structure. Furthermore, the detection of its mRNA in many tissues (kidneys, large intestine, endometrium, bones, vascular smooth muscle cells) has stimulated the studies on the usefulness of PAPP-A measurements in the course of various diseases not associated with pregnancy [2–5]. From the biochemical point of view, PAPP-A is classified as a zinc-binding protease belonging to the family of metalloproteinases. It is secreted by numerous cells, such as: fibroblasts, vascular smooth muscle cells, osteoblasts, trophoblast cells, and, in small amounts, by vascular endothelial cells [5–10].

There are several assays to determine PAPP-A concentrations. It is necessary to choose an adequate method, since, in physiological conditions, the concentration of PAPP-A in adult males and non-pregnant females is very low. Moreover, in pregnant women the protein is present mainly as a heterotetramer (i.e. complexed with major basic protein), while in patients with acute coronary syndrome the non-complexed homodimer, or free PAPP-A, dominates [2, 3, 6, 9, 10].

A significantly increased serum PAPP-A concentrations were observed in patients with severe atherosclerosis, in the course of acute coronary syndromes connected with the plaque rupture, as well as in the course of kidney diseases [3, 9–11]. The increase of PAPP-A in end-stage renal disease patients treated with maintenance hemodialysis, and the prognostic value of PAPP-A for the assessment of long-term outcome in hemodialysis patients, were first reported in 2003. It was observed that the concentrations of PAPP-A in dialysis patients are, on average, three times higher than in healthy population (both the free and complexed forms of PAPP-A are increased); however, these values are nearly 100–1000 lower than the values registered in the first trimester of pregnancy [2–7]. Additionally, patients treated with hemodialysis tended to have higher PAPP-A than those undergoing peritoneal dialysis [3, 12]. Importantly, some authors observed the changes in PAPP-A concentrations during a single hemodialysis session. PAPP-A increased in the early phase of a hemodialysis session, and subsequently, it normalized by the end of the session. The initial increase in PAPPA-A was attributed to the possible influence of heparin [8, 13].

On contrary, in one of recent studies, Abdel-Messeih *et al.* [14] observed that a significant increase in the concentration of PAPP-A occurs proportionally to the duration of dialysis, and consequently, referred to PAPP-A as a new acute-phase protein. The increase in PAPP-A during a dialysis session may result from the production of PAPP-A due to the contact with synthetic dialysis membranes, or due to the release of PAPP-A from vascular endothelial cells [14]. A contact of blood with dialysis membranes leads to the activation of circulating neutrophils and monocytes. This, in turn, stimulates the production of reactive oxygen species and cytokines, and leads to chronic inflammation [15]. Moreover, numerous interesting correlations between PAPP-A and placental growth factor, matrix metalloproteinases

MMP-2 and MMP-9, cardiac markers, such as troponin (cTnI) or brain natriuretic protein (BNP), as well as serum creatinine were observed in dialysis patients [2, 7, 16]. In patients with chronic kidney disease (CKD), the concentration of PAPP-A is significantly reduced after kidney transplantation, and it correlates with the function of the transplanted organ [4].

The aim of this study was to evaluate the diagnostic usefulness of PAPP-A serum concentrations in CKD patients treated with maintenance hemodialysis and its relationships with the duration of dialysis treatment. In particular, the study investigated the associations between serum PAPP-A and the results of laboratory tests performed in order to monitor health status in hemodialysed patients, i.e. complete blood counts and the markers of iron metabolism, N-terminal pro-brain natriuretic peptide (NT-proBNP), the markers of electrolyte and mineral homeostasis, as well as the markers of inflammation and nutritional status.

Materials and methods

The study included 78 consecutive patients with CKD stage G5, receiving maintenance hemodialysis treatment at the Department of Nephrology, Jagiellonian University Medical College in Cracow, Poland. The patients' mean age was 57.1 ± 14.3 years (range: 20 to 83 years) and median duration of hemodialysis treatment was 60 months (range: 12–360 months). All patients received 4-hour dialysis sessions 3 times a week, using polysulphone dialyzers and low molecular weight heparin anticoagulation. Only patients with stable disease course for at least 3 months were included. Patients with diabetes, any acute conditions, or neoplasm were excluded. The study protocol was approved by the Bioethical Committee of the Jagiellonian University in Cracow, Poland. Each patient has given the written informed consent for the study.

Blood samples for laboratory tests were drawn from the arteriovenous fistula or from the dialysis catheter before initiation of the dialysis session and, importantly, before administration of heparin. K2-EDTA anticoagulated whole blood samples were used for complete blood counts. Serum samples were used for biochemical and immunochemical tests.

The complete blood counts were performed using the 5-diff Sysmex XE 2100 automatic hematology analyzer. The routine biochemical and immunochemical tests, i.e. albumin, urea, intact parathormone (iPTH), iron, unsaturated iron binding capacity (UIBC) and total iron binding capacity (TIBC), enzymes (alanine and aspartate aminotrasferase, alkaline phosphatase), sodium, potassium, total calcium, and phosphate were carried out using the Cobas 6000 automatic analyzer (Roche Diagnostica, Mannheim, Germany). PAPP-A concentrations were measured by *electrochemiluminescence* immunoassay (*ECLIA) with Cobas e601 analyzer (*Roche Diagnostica, Mannheim, Germany). Serum prealbumin (PRE), C-reactive protein (CRP), alpha-1-acid glycoprotein (AAG) were measured using BN II Nephelometer (Siemens Healthcare Diagnostics, Germany).

In addition, the following indices of nutritional status were calculated: Cancer Serum Index (CSI), CRP/PRE, Prognostic Inflammatory and Nutrition Index (PINI) and Glasgow Prognostic Score (GPS), using the following formulas: CSI = AAG [g/L] / PRE [g/L] [17]; GPS = 0 was assumed for CRP <10 mg/L and albumin >35 g/L; GPS = 1 for CRP >10 mg/L and albumin >35 g/L; and GPS = 2 for CRP >10 mg/L and albumin <35 g/L [18]; PINI = (CRP × AAG) / (albumin × PRE) [19].

Statistical analysis

Qualitative data are presented as a number of patients in a given category and the percentage of the appropriate group. Qualitative data are shown as mean ± standard deviation or median (25–75 percentile), depending on distribution as tested with Shapiro-Wilk's test. The differences between groups were tested using t-test or the Mann-Whitney test. The correlations were assessed using Pearson's coefficient, after the logarithmic transformation (natural logarithm — ln) of right-skewed variables. The multiple linear regression was adjusted for age and sex. The results were considered statistically significant at $p<0.05$. Calculations were performed using Statistica 10.0 (StatSoft) software.

Results

The median PAPP-A concentrations in hemodialyzed patients were almost two times higher than the upper reference limit (Table 1), however, the maximum values in the studied group reached 14-times the upper reference limit, i.e. 140 mIU/L. The studied group was divided according to the duration of dialysis treatment, the median duration of hemodialysis was 60 months. There were no statistically significant differences regarding the clinical data and the results of laboratory tests between the patients dialyzed for shorter and for longer periods (Table 1).

Associations between serum PAPP-A and blood counts and iron homeostasis

In studied patients, the average concentrations of hemoglobin (Hgb), the value of hematocrit (Hct) and the number of red blood cells (RBC) were low comparing to the reference ranges, although the average Hgb concentrations fell within the target range, as proposed by KDIGO (Table 1). RBC, Hct and Hgb values were lower than corresponding reference values in, respectively, 92%, 84% and 94% of men, and 56%, 96% and 70% of women. The mean RDW-CV value was higher than the upper reference limit, reflecting mild anisocytosis in most patients.

Median iron concentrations and UIBC values were within the respective reference ranges, while TIBC values were around the lower reference limit, irrespective of the duration of dialysis therapy (Table 1).

No correlations were observed between serum PAPP-A concentrations and the parameters of complete blood counts. Also, there were no statistically significant correlations between ln (PAPP-A) and the markers of iron metabolism, although some tendency toward negative correlations with TIBC and UIBC was observed, especially among longer dialyzed patients (Table 2).

Association between serum PAPP-A and NT-proBNP

The median concentrations of NT-proBNP in hemodialyzed patients were 30–40-times higher comparing with reference limit (Table 1). Significant positive correlation was observed between ln (PAPP-A) and ln (NT-proBNP) in the whole group of patients and in the subgroup dialyzed for ≤ 60 months (Table 2). In multiple regression, this association was independent of age and sex of patients (beta = 0.32 ± 0.14; p = 0.034).

Table 1. Clinical and selected laboratory data in hemodialyzed CKD patients.

Variables	Patients dialyzed for ≤60 months (N = 39)	Patients dialyzed for >60 months (N = 39)	p-values	Reference intervals/ target values
Male gender [N/(%)]	26 (67)	25 (64)	0.9	–
Age [years]	58 ± 11	57 ± 15	0.9	–
Hemodialysis vintage [months]	36 (24–48)	168 (84–210)	<0.001	–
BMI [kg/m^2]	25.7 ± 3.7	23.9 ± 4.3	0.1	18.5–24.9
WBC [10^3/μL]	6.73 ± 2.22	6.67 ± 1.53	0.9	4.0–10.0
RBC [10^6/μL]	3.58 ± 0.45	3.59 ± 0.58	0.9	F: 3.5–5.0/M: 4.5–6.5
Hemoglobin [g/L]	10.7 ± 1.6	10.6 ± 1.4	0.9	F: 11.0–15.0/ M: 12.0–17.0 / 9.0–11.5 [23]*
Hematocrit [%]	33.0 ± 4.8	33.0 ± 4.4	0.7	F: 37.0–47.0/ M: 40.0–54.0
MCV [fL]	92.3 ± 5.4	92.5 ± 4.8	0.6	82.0–92.0
MCH [pg]	29.8 ± 2.0	29.6 ± 1.6	0.7	27.0–31.0
MCHC [g/L]	32.3 ± 0.9	32.0 ± 0.8	0.1	32.0–36.0
RDW-CV [%]	14.7 ± 1.6	14.6 ± 1.3	0.7	12.1–14.1
PLT [10^3/μL]	191 (164–244)	238 (182–280)	0.1	150–350
Urea [mmol/L]	23.74 ± 5.17	22.5.40	0.3	2.76–8.07
Iron [μmol/L]	13.2 (10.7–14.9)	11.0 (9.65–13.7)	0.1	5.83–34.50
UIBC [μmol/L]	31.2 (25.1–34.6)	28.2 (23.7–34.8)	0.6	F: 24.2–70.1/ M: 22.3–61.7
TIBC [μmol/L]	41.8 (37.8–49.2)	38.7 (34.9–47.4)	0.2	40.80–76.60
Transferrin saturation [%]	29.9 (24.4–35.5)	27.7 (23.1–32.9)	0.1	<30 [23]*
iPTH [ng/mL]	401 (144–664)	301 (132–488)	0.4	15.0–65.0/ 130–585 [26]**
Calcium [mmol/L]	2.08 ± 0.20	2.10 ± 0.21	0.8	2.15–2.55
Phosphate [mmol/L]	1.94 ± 0.62	1.97 ± 0.57	0.8	0.81–1.45
Potassium [mmol/L]	5.31 ± 0.72	5.52 ± 0.57	0.1	3.50–5.10
Sodium [mmol/L]	139.3 ± 2.9	139.3 ± 2.2	0.9	136.0–145.0
Albumin [g/L]	32.1 ± 7.1	34.5 ± 6.4	0.1	35.0–50.0
Prealbumin [g/L]	0.37 ± 0.11	0.38 ± 0.11	0.5	0.2–0.4
CRP [mg/L]	3.72 (1.5–8.76)	5.32 (3.24–15.1)	0.1	0.16–5.00
AAG [g/L]	1.27 ± 0.25	1.23 ± 0.31	0.5	0.5–1.2
PINI	0.38 (0.15–1.23)	0.45 (0.22–1.83)	0.4	<1

Variables	Patients dialyzed for ≤60 months (N = 39)	Patients dialyzed for >60 months (N = 39)	p-values	Reference intervals/ target values
CSI	3.27 (2.72–4.76)	3.10 (2.67–3.80)	0.3	–
GPS: 0/1/2 [N/(%)]	29 (74)/9 (23)/1 (3)	22 (56)/10 (26)/7 (18)	0.1	0
CRP/PRE	0.009 (0.003–0.030)	0.013 (0.008–0.043)	0.1	–
NT-proBNP [pg/mL]	3851 (731–23037)	5119 (2049–9563)	0.6	<125
PAPP-A [mIU/L]	18.0 (14.0–23.0)	18.0 (15.0–22.0)	0.7	4.0–10.0

*The range of expected values by KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease [23]; **KDIGO Clinical Practice Guidelines for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease — Mineral and Bone Disorder (CKD-MBD) [26]; WBC — white blood cells; RBC — red blood cells; MCV — mean corpuscular volume; MCH — mean corpuscular hemoglobin; MCHC — mean corpuscular hemoglobin concentration; RDW — red distribution width; PLT — platelets; TIBC — total iron-binding capacity; UIBC — unsaturated iron-binding capacity; CRP — C-reactive protein; AAG — acid alpha 1 glicoprotein; PINI — Prognostic Inflammatory and Nutritional Index; GPS — Glasgow Prognostic Score; PRE — prealbumin; CSI — Cancer Serum Index; NT-proBNP — N-terminal pro-brain natriuretic peptide; PAPP-A — pregnancy-associated plasma protein A

Table 2. Correlations between ln (PAPP-A) and selected variables in hemodialyzed CKD patients.

Variables	Total cohort (N = 78)		Patients dialyzed for ≤60 months (N = 39)		Patients dialyzed for >60 months (N = 39)	
	R	p-values	R	p-values	R	p-values
Sodium	0.28*	0.020	0.31	0.065	0.50*	0.002
Potassium	0.17	0.2	0.23	0.2	–0.09	0.5
Calcium	0.01	0.9	–0.06	0.7	–0.12	0.4
Phosphate	0.10	0.4	0.13	0.4	–0.14	0.4
ln (PTH)	0.06	0.6	0.01	0.9	0.06	0.7
ln (iron)	–0.01	0.9	–0.01	0.9	0.16	0.3
UIBC	–0.21	0.076	–0.22	0.2	–0.32	0.056
TIBC	–0.22	0.054	–0.22	0.2	–0.29	0.085
ln (transferrin saturation)	0.12	0.3	0.12	0.5	0.30	0.1
ln (CRP)	0.18	0.1	0.40*	0.023	–0.09	0.6
GPS	0.13	0.3	0.38*	0.030	–0.26	0.1
ln (CRP/PRE)	0.19	0.1	0.42*	0.021	–0.12	0.5
ln (CSI)	0.10	0.4	0.29	0.086	–0.21	0.2
ln (PINI)	0.15	0.2	0.36*	0.046	–0.13	0.4
ln (NT-proBNP)	0.24*	0.045	0.37*	0.026	0.11	0.5

*Statistically significant correlations; PTH — parathormon; UIBC — unsaturated iron-binding capacity; TIBC — total iron-binding capacity; CRP — C-reactive protein; GPS — Glasgow Prognostic Score; PRE — prealbumin; CSI — Cancer Serum Index; PINI — Prognostic Inflammatory and Nutritional Index; NT-proBNP — N-terminal pro-brain natriuretic peptide

Associations between serum PAPP-A and the markers of electrolyte and mineral homeostasis

In studied patients, serum concentrations of potassium were high, while sodium fell within the reference ranges (Table 1). Serum sodium positively correlated with ln (PAPP-A) in the whole group of patients, and in particular among those with long dialysis therapy duration (Table 2). Also, serum potassium positively correlated with PAPP-A among studied men (R = 0.52; p <0.001; Fig. 1a).

Also, serum concentrations of phosphate and iPTH were high, whereas calcium concentrations were low in most patients as compared to the reference intervals. The majority of patients had iPTH concentrations within the target values recommended by KDIGO. No significant correlations were observed between calcium, phosphate and iPTH and serum PAPP-A concentrations, irrespective of dialysis therapy duration (Table 2). However, there was positive correlation between ln (PAPP-A) and phosphate among studied man (R = 0.34; p = 0.026; Fig. 1b).

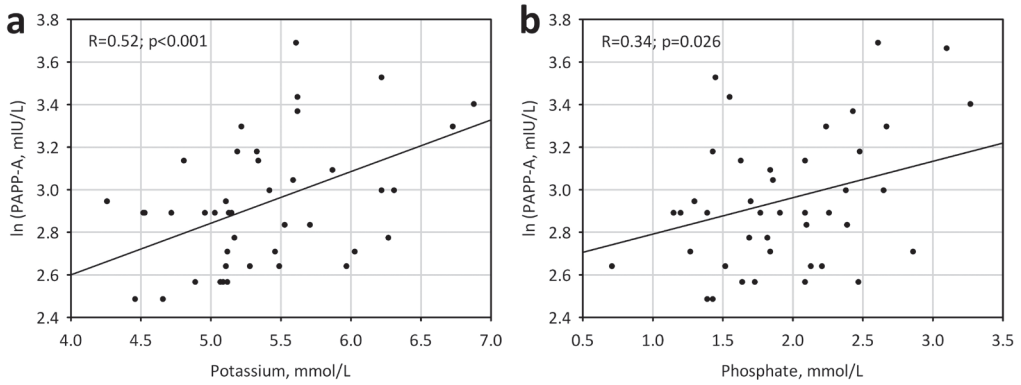

Fig. 1. The associations between serum PAPP-A concentrations and serum potassium (a) and phosphate (b) in men treated with maintenance hemodialysis.

Associations between serum PAPP-A and the markers of inflammation and nutritional status

The average BMI values fell within the normal range (Table 1). We observed low albumin concentrations in studied patients (Table 1); 54% of them had albumin concentrations below 35 g/L. In 19% of patients, albumin concentration fell within the range of 25–29 g/L, and in 14% of patients it was ≤24 g/L (i.e. the values associated with severe malnutrition). Additionally, 7.6% of patients had low PRE concentrations. CRP concentrations were high, especially in patients with longer dialysis therapy duration (Table 1). Also, most patients have AAG concentrations exceeding upper reference limit (Table 1).

The values of nutritional indices are shown in Table 1. PINI>1 was noted in 31% of patients, 35% had higher GPS values (1 or 2). The maximum values of nutritional parameters were as follows: CSI 9.09; PINI 14.10; and CRP/PRE 0.255. The CSI and PINI values

were significantly higher in women than in men (median 3.6 vs 2.9; p <0.001 and 0.9 vs 0.3; p <0.003, respectively).

In patients undergoing hemodialysis treatment for ≤60 months, ln (PAPP-A) significantly, positively correlated with ln (CRP), GPS, ln (CRP/PRE) and ln (PINI) (Table 2).

Discussion

Despite the significant advancements in dialysis treatment, it is still associated with high mortality, and hence, it is far from being ideal. It is estimated that mortality is nearly 9 times higher among CKD patients undergoing maintenance dialysis than among general population. About one half of deaths among dialysed patients are caused by cardiovascular causes [6, 8, 20]. Frequently, sudden deaths are caused by the ventricular arrhythmias associated with hemodialysis procedure, i.e. sudden changes in potassium concentrations or volemia [21]. However, many chronic factors such as: anemia, mineral and bone disorders, or the malnutrition-inflammation-atherosclerosis (MIA) syndrome contribute to cardiovascular morbidity and mortality [3, 22].

In patients with cardiovascular events and the recognized renal failure, high PAPP-A concentrations were observed [14]. Also, Coskun A *et al.* [12] observed significantly higher PAPP-A concentrations among hemodialyzed patients than among healthy controls [12]. The latter study made an attempt to find correlations between PAPP-A concentration and the main factors influencing morbidity and mortality in hemodialyzed patients. Taking into account the differences in methods used to measure PAPP-A concentrations, the levels of PAPP-A observed in the mentioned studies were comparable to what was observed in our patients (average values about 1.5–2.5 times higher than control values). The increase in PAPP-A concentration has been considered an indicator of a significant damage to endothelial cells, and of an increased risk of death in dialyzed patients [2, 5].

Patients enrolled in our study were mostly adult men with normal weight or overweight. We observed normocytic anemia with high anisocytosis values (yet with Hgb concentrations within the recommended target range for dialysis patients); secondary hyperparathyroidism with accompanying hyperphosphatemia and hypocalcemia (typical for hemodialysis patients); hyperkalemia; increased CRP (mainly in those dialyzed for longer periods) and low concentrations of serum albumin. We observed no differences in laboratory data between patients hemodialyzed for shorter and longer periods, however, different correlations of PAPP-A were shown in those two groups of patients.

In patients dialyzed longer than 60 months, a positive association was observed between serum PAPP-A and serum sodium. To our knowledge, such association has not been previously reported. KDIGO [23] recommends that the intake of sodium chloride in CKD patients should not exceed 5 g per day. High sodium intake, particularly by patients without residual diuresis, is a risk factor for high blood pressure and it contributes to excess water accumulation between dialysis sessions. Hypervolemia is, in turn, one of the major causes of heart failure in hemodialyzed patients. Interestingly, we also observed positive association between PAPP-A and potassium concentrations in men.

On the other hand, in the group of patients with shorter dialysis treatment, PAPP-A positively correlated with NT-proBNP — the serum biomarker of heart failure. Natriuretic peptides (e.g. BNP), which control the water and sodium balance and maintain the cardiovascular homeostasis, are released by cardiomyocytes stretched due to the increase in the preload or afterload (e.g. in the case of excess water accumulation) [24, 25]. Kalusova *et al.* [5], observed that in a group of 261 patients receiving maintenance dialysis, the concentrations of natriuretic peptides were significantly higher than among healthy controls. Additionally, these authors observed a correlation between PAPP-A and the total mortality caused mainly by cardiovascular events [5].

Another finding of our study is the positive association between serum PAPP-A and CRP, as well as the indices of poor nutritional status, i.e. GPS, CRP/PRE and PINI, in patients dialyzed for ≤ 60 months. This observation should encourage clinicians to look for the causes of malnutrition and inflammatory states in dialysis patients. Malnutrition may result from clinically significant loss of proteins in the course of nephrotic syndrome in patients with preserved residual diuresis, or from lack of appetite in uremic patients. However, the increase in the values of inflammatory markers and indices of malnutrition/inflammation may in many cases be due to late initiation of hemodialysis (because of poor availability of specialist care by nephrologist, or delayed consent of the patient to dialysis treatment, or delayed diagnosis of CKD). In addition, the restrictions in protein intake in advanced CKD (less than 0.8 g/kg body weight/day according to KDIGO), meant to prevent hyperphosphatemia and secondary hyperparathyroidism, may also account for malnutrition [26].

The positive correlation between PAPP-A and CRP in our study agrees with the observation by Kalousova *et al.* [5], according to whom, in dialysis patients, PAPP-A is not only an independent biomarker of total mortality, but also of mortality caused by infections [2, 5, 7]. CRP is a recognized marker of inflammatory states; it changes dynamically depending on the patient's clinical condition. Hemodialysis patients are especially vulnerable to infections. Additionally, the chronic inflammatory state is one of the factors that constitute the MIA syndrome.

Finally, we did not observe the correlation between PAPP-A and iPTH, as reported by Coskun *et al.* [12]. However, PAPP-A positively correlated with serum phosphate in men. The differences in patients' characteristic and the different method of PAPP-A measurement may be in part responsible for the discrepancy.

Although limited by the low number of patients, our study point towards the usefulness of PAPP-A as a marker associated with cardiovascular dysfunction, inflammatory states and malnutrition in hemodialyzed patients.

Conclusions

In hemodialysis patients the average serum PAPP-A concentrations were significantly increased. In patients with shorter dialysis vintage, PAPP-A correlated with NT-proBNP, as well as with the markers of inflammatory state and malnutrition. On the other hand, in patients with longer duration of hemodialysis therapy, PAPP-A positively correlated with serum sodium. Taking into account the published associations between PAPP-A and mortality, it

seems reasonable to restrict the intake of fluids and salt in dialyzed patients. Additionally, the restrictions in protein should take into account the patient's nutritional status. Summarizing, serum PAPP-A seems a useful biomarker associated with cardiovascular dysfunction, inflammatory states and malnutrition in hemodialysis patients.

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Conflict of interest

No declared.

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