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The Significance of Pregnancy-associated Plasma Protein a Serum Concentration in Clear Cell Renal Cell Carcinoma

MARCELA CECHOVA[1], MATUS CHOCHOLATY[1], TOMAS ZIMA[2], MAREK BABJUK[1] and MARTA KALOUSOVA[2]

[1]*Department of Urology, University Hospital Motol, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic;*
[2]*Institute of Medical Biochemistry and Laboratory Diagnostics, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, Czech Republic*

Abstract. *Background/Aim: Proteinase pregnancy-associated plasma protein A (PAPP-A) modulates the cell growth and carcinogenesis process. Its role in clear cell renal cell carcinoma (ccRCC) remains unclear. This study aimed to evaluate the significance of PAPP-A serum concentration in diagnosis, follow-up and prognosis of ccRCC patients. Materials and Methods: In a prospective study including 121 patients who underwent radical or partial nephrectomy for ccRCC [localized ccRCC without relapse (n=80), localized ccRCC with later relapse (n=26), primary metastatic cancer (n=15)] PAPP-A serum concentration was assessed preoperatively and in certain subgroups also postoperatively. Results: PAPP-A serum concentration showed no statistically significant difference between ccRCC and controls and among ccRCC subgroups, respectively. Disease stage and Fuhrman's grade were not shown to affect PAPP-A concentration. The dynamics of postoperative PAPP-A concentrations did not reveal any significance and PAPP-A was not a prognostic factor for cancer related or overall survival. Conclusion: PAPP-A serum concentration does not seem to be a useful biomarker in ccRCC.*

Renal cell carcinoma (RCC) accounts for 2-3% of all adult malignancies presenting the highest incidence in the Western world (1). Incidence of RCC has been continuously increasing over the last years. Clear cell RCC (ccRCC) represents the most prevalent histopathological subtype, which is diagnosed in more than 80% of patients. The exact process of the formation and progression of ccRCC in not known. There are no recommended genetic or biochemical markers for diagnosis and prediction of relapse before surgical removal of the tumour or during follow-up.

Despite advances in diagnosis, especially in imaging techniques and higher rates of incidentally diagnosed tumours with imaging for unrelated complaints, still, in up to 30% of patient's, distant metastases are present at the time of initial diagnosis (2, 3). Furthermore, recurrence occurs in 20-30% patients with an initially localized disease during the follow-up (4). RCC is potentially curative with surgery and it is generally resistant to chemotherapy and radiotherapy. Despite progress in targeted therapy, prognosis of metastatic RCC remains poor with median survival less than one year (3). Therefore, detection of a biomarker suitable for early diagnosis and, even more, for accurate determination of the risk of relapse after partial or radical nephrectomy is of great importance.

Pregnancy-associated plasma protein A (PAPP-A), also referred to as pappalysine-1 is a proteolytic enzyme that belongs to the zinc metalloproteinase superfamily. PAPP-A increases bioavailability of insulin like growth factor 1 (IGF-1) for receptor activation *via* proteolysis of inhibitory IGF binding proteins (IGFBPs), in particular IGFBP-4. Targeting IGF-1 receptor (IGF-1R) IGF-1 affects proteosynthesis (5). PAPP-A is expressed predominantly during pregnancy in placental syncythiotrophoblast and is required for normal foetal development and growth. Routinely, measurement of serum concentration of PAPP-A applies as a screening method for Down syndrome in the first trimester of gestation.

However, despite during pregnancy, PAPP-A is also expressed by multiple tissues and has an important role in processes like wound healing, vascular repair or bone remodelling. The involvement of the proteolytic effect of PAPP-A in the process of carcinogenesis is highly suggested

Correspondence to: Prof. Marta Kalousová, MD, Ph.D., Institute of Medical Biochemistry and Laboratory Diagnostics, General University Hospital and 1st Faculty of Medicine, Charles University, Prague, 12808 Prague 2, U Nemocnice 2, Czech Republic. Tel: +420 224964212, e-mail: marta.kalousova@lf1.cuni.cz

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and has been extensively studied in the past years. So far, increased serum concentration of PAPP-A has been described in lung and ovarian cancer and even more, overexpression of PAPP-A has been shown to promote cancer growth and increase cancer aggressiveness in breast and ovarian cancer (6-9).

The role of PAPP-A in RCC remains unclear. The present study aimed to assess PAPP-A serum concentration in subjects suffering from ccRCC and to evaluate its significance in diagnosis, follow-up and assessment of prognosis, which has not been evaluated yet.

Materials and Methods

Characteristics of study population. In our study we enrolled 121 patients (78 men, 43 women, mean age 63.4±10.52 years) that were subjected to radical or partial nephrectomy due to ccRCC from July 2011 to August 2015. Negative surgical margins on histopathological specimens of resected tumours were described in all individuals. ccRCC patients were classified into three subgroups: subjects with localized ccRCC without relapse (lccRCC, n=80), subjects with localized ccRCC with later relapse (rccRCC, n=26) and subjects with primary metastatic cancer (mccRCC, n=15). Staging was performed according to the 2009 TNM classification system and Fuhrman classification was used to define the nuclear grade. Surveillance following surgical treatment was performed according to the EAU Guidelines for Renal Cell Carcinoma (10). Median follow-up was 4.6 years. The parameters of the subjects with ccRCC are shown in Table I.

PAPP-A serum concentration was assessed in all individuals preoperatively and in lccRCC (n=23 patients) and rccRCC (n=14 patients) subgroups 3 weeks and 3 months postoperatively.

The control group consisted of 69 healthy subjects (35 men, 34 women, mean age 58.13±4.7 years), who underwent basic uro-oncological screening including ultrasound, urine cytology and measurement of PSA levels in men. None of them had a history of any oncological disease.

The present study was performed in adherence to the principles stated in the Helsinki Declaration and approved by the institutional review board and ethics committee. Prior to entering the study, all participants gave their informed consent.

PAPP-A serum concentration was assessed by TRACE (Time Resolved Amplified Cryptate Emission) using standard kits and Kryptor analyzer (Brahms GmbH, Thermo Fisher Scientific, Henningsdorf, Germany). Results are expressed in mIU/l. One IU/l is equivalent to 4500 ng/ml (11).

Statistical analysis. All data are expressed as the mean±standard deviation (SD) for continuous variables and percentages for categorical variables. For continuous variables, the difference between two groups was analysed by the Mann-Whitney *U*-test or one-way ANOVA test, as appropriate. For the analysis of continuous variables over time, the repeated measures ANOVA test was used. Survival analysis was performed using the Kaplan–Meier method. To compare survival between patient groups or subgroups the log-rank test was applied. Univariate Cox proportional hazards regression analyses were used to evaluate PAPP-A as a potential predictor of overall (OS) and cancer specific survival (CSS). At $p<0.05$ results were considered statistically significant. All statistical analyses were performed using MedCalc (version 13, Ostend, Belgium).

Table I. *Clinical parameters of ccRCC cases*

Number of patients (men/women)	121 (78/43)
Age (years)	63.4±10.52
Stage	
I	78 (64.4%)
II	4 (3.3%)
III	24 (19.8%)
IV	15 (12.4%)
Grade	
1	36 (29.8%)
2	59 (48.8%)
3	18 (14.9%)
4	8 (6.6%)

Table II. *PAPP-A serum concentrations*

PAPP-A serum concentration (mIU/l)	RCC patients			Controls
	8.74±3.5			8.24±2.3
	lccRCC	rccRCC	mccRCC	
Preoperative	8.76±3.7	8.72±3.1	8.7±3.4	
3 weeks after surgery	9.08±3.5	8.27±3.2		
3 months after surgery	9.39±3.8	9.33±3.1		

Results are not statistically significant.

Results

Our results did not show any statistically significant difference in PAPP-A serum concentration between subjects with ccRCC (8.74±3.5 mIU/l) and control group (8.24±2.3 mIU/l), $p=0.24$. In addition, no statistically significant difference among lccRCC (8.76±3.7 mIU/l), rccRCC (8.72±3.1 mIU/l) and mccRCC (8.7±3.4 mIU/l) subgroups was found ($p=0.99$). Furthermore, no statistically significant difference in PAPP-A serum concentration was observed even after subdivision of subjects based on tumour stage and Fuhrman's grade ($p=0.76$, $p=0.61$). The dynamics of PAPP-A concentrations at 3 weeks and 3 months postoperatively did not reveal any significant difference in lccRCC (9.08±3.5 vs 9.39±3.8 mIU/l, $p=1.00$) or rccRCC (8.27±3.2 *vs*. 9.33±3.1 mIU/l, $p=0.43$) subgroups. PAPP-A serum concentrations are depicted in Table II.

The median value of PAPP-A serum concentration was used in the survival analysis. Preoperatively, the median was 8.2 mIU/l and 3 months after the surgery was 9.2 mIU/l. Preoperative and 3 months after surgery PAPP-A serum concentration was not a prognostic factor for CSS or OS (Table III).

Table III. *Cancer-specific and overall survival in patients with localized ccRCC.*

Cancer-specific survival in patients with localized ccRCC					
	Median PAPP-A serum concentration (mIU/l)	Number of patients	Relapse	HR (CI)	*p*-Value
Preoperative	<8.2	53	14 (26.4%)		
	≥8.2	53	12 (22.2%)	1.08 (0.5-2.35)	0.84
3 months after surgery	<9.2	18	6 (33.3%)		
	≥9.2	19	8 (42.1%)	0.47 (0.16-1.37)	0.14
Overall survival in patients with localized ccRCC					
	Median PAPP-A serum concentration (mIU/l)	Number of patients	Exitus	HR (CI)	*p*-Value
Preoperative	<8.2	53	14 (26.4%)		
	≥8.2	53	8 (14.81%)	1.85 (0.8-4.29)	0.15
3 months after surgery	<9.2	18	5 (26.3%)		
	≥9.2	19	7 (38.9%)	0.59 (0.19-1.87)	0.38

HR: Hazard ratio; CI: confidence interval. Results are not statistically significant.

Discussion

In this study, for the first time, the significance of PAPP-A serum concentration in diagnosis and follow-up of ccRCC was evaluated.

PAPP-A, a well-known protease, modulates cell growth through increasing local availability of IGF-1 for receptor binding and activation. IGF-1R stimulation has been proven to initiate malignant transformation promoting cell proliferation, dedifferentiation and inhibiting apoptosis (12-14). A range of studies has demonstrated an association between elevated circulating levels of IGF-1 or overexpression of IGF-1R and the risk of developing various tumours including breast, prostate and ovarian cancer (15-17). Therefore, several compounds targeting IGF axis have been tested for cancer therapy (18). Regarding kidney carcinoma multiple publications have confirmed the role of IGF-1 and IGF-1R in the development of RCC (19, 20). Parker *et al*. (21) have demonstrated that expression of IGF-1R may have a negative prognostic role in patients with ccRCC. Additionally, IGF-1R positivity has been shown to correlate with tumour grade and poorer prognosis (22). Interestingly, ccRCC cells with high expression of IGF-1R show higher resistance to chemotherapeutic agents compared to cells with low receptor expression (23).

The role of the proteolytic function of PAPP-A has been implicated in the growth of various cancers. Elevated levels of circulating PAPP-A have been described in patients with lung cancer and even more, the proteolytic activity of PAPP-A was shown to accelerate growth of lung cancer *in vivo* (6, 24). Mansfield *et al*. (8) have showed a higher PAPP-A expression in human breast cancer cells, predominantly in its aggressive forms. In addition, several publications have shown that cancer growth and metastases can be prevented by modulating PAPP-A proteolytic activity. Higher expression of proteolytically active PAPP-A molecules in an ovarian cancer cell line has been found to accelerate cancer growth and has also been correlated with cancer aggressiveness *in vivo* (9). Mikkelsen *et al*. (25) have first demonstrated that monoclonal antibodies targeting PAPP-A (mAb-PA) efficiently inhibit lung cancer tumour growth (25). Furthermore, PAPP-A has been shown to be overexpressed in human ovarian tumours and treatment of mice models with mAb-PA caused a reduction in tumour growth and ascites burden (26). Therefore, assessment of PAPP-A levels in serum or ascites might be used as a biomarker to identify patients that will respond to anti-PAPP-A and anti-IGF, respectively (26, 27). Conversely, PAPP-A knock-out mice have a significant delay in the occurrence of neoplasia (28). PAPP-A has also been identified as a migration-promoting gene in breast cancer, malignant pleural mesothelioma and malignant melanoma (9, 29, 30).

Still, the role of PAPP-A in RCC remains unclear. Since PAPP-A indirectly contributes to the availability and activity of IGF-1, which affects RCC, PAPP-A serum concentration in subjects suffering from ccRCC was evaluated.

However, our results did not meet our expectations. No significant difference was found in PAPP-A serum concentration between subjects with ccRCC and the control group. Also, the difference in PAPP-A serum concentration after

subdivision of ccRCC subjects (lccRCC, rccRCC and mccRCC) did not reach statistical significance. In addition, no statistically significant difference in PAPP-A serum concentration was found even after subdivision of subjects based on tumour stage and Fuhrman's grade. The dynamics of PAPP-A postoperative concentrations didn't reveal any significance and no impact on cancer related or overall survival was observed.

Based on the current results, PAPP-A serum concentration does not seem to be a useful biomarker for diagnosis, follow-up or prediction of prognosis in subjects suffering from ccRCC. Therefore, further research must be done to identify a suitable biomarker for ccRCC. An abundance of potential biomarkers can be found in the literature, yet none has been introduced into routine practice. Until now, no suitable biomarker has been found for the early diagnosis and follow-up of RCC that would have a potential of commercial development and extensive use; this remains the task of further studies.

In conclusion, the significance of PAPP-A serum concentration was evaluated in patients with ccRCC. Although, the role of PAPP-A in carcinogenesis of various tumours has been examined, to the best of our knowledge, our current work assesses for the first time the association between PAPP-A serum concentration and ccRCC. Although PAPP-A appears to be a promising marker for many tumours, our results did not show any significance of PAPP-A serum concentration in subjects with ccRCC in comparison to the control group. In addition, the dynamics of postoperative PAPP-A serum concentration showed no statistical significance. Therefore, PAPP-A does not seem to be a useful biomarker for diagnosis, follow-up and prediction of prognosis in subjects suffering from ccRCC.

Conflicts of Interest

No potential conflicts of interest with respect to the research, authorship and publication of this article exist.

Authors' Contributions

Marcela Cechova, MD has contributed with conceptualization, data curation, formal analysis, project administration, writing - original draft. Matus Chocholaty, MD, PhD has contributed with conceptualization, data curation, formal and statistical analysis, project administration, validation and writing – review and editing. Prof. Tomas Zima, MD, PhD has contributed with supervision of the laboratory part of the study, writing - review and editing. Prof. Marek Babjuk, MD, PhD has contributed with supervision of the clinical part of the study, writing - review and editing. Prof. Marta Kalousova, MD, PhD has contributed with conceptualization, methodology, data analysis, supervision, validation and writing – review and editing.

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