Review

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Pregnancy associated plasma protein-A: a promising biomarker in kidney diseases

https://doi.org/10.1515/tjb-2024-0241
Received September 23, 2024; accepted March 19, 2025;
published online September 30, 2025

Abstract: Kidney diseases are a worldwide public health problem with more than 850 million patients all over the world. Therefore, early diagnosis is essential for effective treatment of any renal disease. Most biomarkers have the potential to be used in diagnosis, screening, prognosis, and follow-up, but it is challenging to confirm associations with certain diseases. Although some biomarkers such as urea and creatinine are used in clinical practice for kidney diseases, these molecules' sensitivity and specificity are not at the desirable level. Pregnancy-associated plasma protein-A (PAPP-A) is being used for the screening of Down's syndrome in the first trimester of pregnancy, however, increased expressions have been reported in various kidney diseases. This study aimed to evaluate the clinical significance of PAPP-A as a potential biomarker for diagnosing and monitoring renal diseases. We searched Pubmed and Web of Science databases using PAPP-A, kidney diseases, acute kidney injury, chronic kidney disease, hemodialysis, peritoneal dialysis, kidney transplant, diabetic nephropathy, polycystic kidney disease, and kidney cancer. According to our search, PAPP-A seems to be a candidate biomarker for diabetic nephropathy and chronic kidney disease, yet further studies are needed to detect diseases in the early stage.

Keywords: kidney diseases; pregnancy-associated plasma protein-A; biomarkers; acute kidney injury; chronic kidney disease; diabetic nephropathy

Introduction

Kidney diseases are a global health problem and according to the World Health Organization, they are the 10th leading cause of death worldwide. Mortality was reported at 1.3 million in 2020, and the statistical analysis emphasizes that it tends to increase [1]. Early diagnosis is essential for effective treatment, prevention of complications, and reduction of mortality rate. Various biomarkers such as creatinine and estimated glomerular filtration rate (eGFR) are being used to manage kidney diseases however these biomarkers are deferred detection markers of kidney damage and unspecific to disease etiology [2]. The serum creatinine concentration exceeds the normal range (0.63–1.16 mg/dL in men, 0.48–0.93 mg/dL in women) [3], it indicates that approximately 50 % of the renal parenchyma has already been damaged [4]. Also, kidney damage occurs when a decrease in kidney function occurs where the glomerular filtration rate (GFR) is below 60 mL/min per 1.73 m^2 [5, 6] (the normal range is higher than 90 mL/min per 1.73 m^2). Novel biomarkers such as beta trace protein (BTP), urinary neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and pregnancy-associated plasma protein A (PAPP-A) have been introduced in clinical practice [6–8]. Elevated PAPP-A levels are found in plasma during the pregnancy period [9]. Although it has been named as 'pregnancy-associated plasma protein', it has been detected in plasma and various tissues of non-pregnant women and men [10]. Elevated PAPP-A levels have been reported in kidney diseases, including chronic kidney disease and diabetic nephropathy [10, 11].

In this review, 1) we summarized the biomarkers that are already being used in kidney diseases and their limitations 2) updated the literature related the role of PAPP-A in

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the path-ophysiology of kidney diseases 3) evaluated the clinical significance of PAPP-A as a potential biomarker for managing different types of kidney diseases.

We searched the PUBMED and Web of Science using the words "Renal Disease", "Kidney Disease" "Pregnancy-associated plasma protein-A"; "Biomarkers"; and evaluated the clinical significance of the PAPP-A in acute kidney injury (AKI), chronic kidney disease (CKD), hemodialysis (HD), peritoneal dialysis (PD), renal transplant (RT), diabetic nephropathy, (DN), polycystic kidney disease (PKD), and kidney cancer. Studies from the last 20 years were included in the search to ensure up-to-date findings.

This review is guided by the Scale for the Assessment of narrative review articles (SANRA) [12].

Kidney diseases

Kidney diseases can generally be defined as the inability of the kidney to fully perform its function, and the underlying causes are quite diverse [13]. Immune-mediated diseases such as glomerulonephritis and lupus nephritis, recurrent urinary tract infections [14], hereditary diseases, renal and urinary tract abnormalities due to fetal malformation, obstructions due to kidney stones or tumors can cause renal dysfunction [13–15].

Kidney diseases can be examined based on the structural changes of glomeruli, tubules, interstitium, and blood vessels. However, some structures of the kidney are more susceptible to specific types of damage. Glomerular diseases are often immunologically induced, whereas tubular and interstitial diseases are most likely caused by toxic and infectious agents [16]. Kidney diseases can reveal quickly, like a sudden decrease in glomerular filtration in AKI [17], or gradually, like in CKD and DN [16, 17]. Regardless of the sources or way of development, without therapeutic administrations all kidney tissue can be damaged and can lead to end-stage kidney disease (ESKD). ESKD also refers to kidney failure, affects approximately 0.1 % of the world's population and in the absence of effective treatment (mainly dialysis or kidney transplant), it is fatal [18]. To prevent or reduce the progression of kidney diseases to kidney failure, the necessity of early diagnosis is essential.

Biomarkers used in the management of kidney diseases

Diagnosis of kidney disease requires analysis of biomolecules in blood and urine [19]. To confirm the diagnosis, serum and urine analysis results should be validated by radiological and pathological examinations.

The main biomarkers are creatinine, urea, albumin, and cystatin C (Table 1) [20] yet, these biomarkers detect kidney diseases in the late stage, or they can give false positive or negative results [21]. Serum creatinine, greater than 1.7 mg/dL had a sensitivity of 12.6 % and a specificity of 99.9 % for the detection of renal failure in over 65+ years people [22]. In addition, urinary BTP with less than 90 mL/min/1.73 m^2 had 75 % sensitivity and 96 % specificity for glomerular filtration rate impairment [23]. Other potential biomarkers such as CKD273 (proteomic biomarker) and pantothenate [24] derived from data obtained from 'omics' platforms are not yet widely applicable due to their complicacy and high costs. There are also numerous novel urinary biomarkers such as kidney injury molecule (KIM-1), neutrophil gelatinase–associated lipocalin (NGAL) and tissue inhibitor of metalloproteinases (TIMP) [6]. Among these biomarkers, PAPP-A has also been identified as potential biomarker. The role of PAPP-A in kidney diseases is evaluated in detail thereafter. A comprehensive summary of biomarkers, sample types, and their association with specific kidney diseases is presented in Table 1, highlighting the potential clinical importance of PAPP-A compared with other markers.

Table 1: Biomarkers are measured in serum and urine for the diagnosis of kidney diseases.

Biomarker	Renal disease	Sample type	Ref.
Cystatin C[a]	AKI, CKD	Serum	[23, 24]
Creatinine[a]	CKD, AKI	Serum/Urine	[6, 24]
Urea[a]	ESKD	Serum/Urine	[25]
BTP[b]	HD	Serum/Plasma	[26]
Type IV collagen	DN	Urine	[27]
KIM-1[b]	AKI, RCC	Urine	[6, 26]
NGAL[b]	DN, AKI, CKD	Serum/Urine	[27, 28]
Podocin[b]	DN	Urine	[29]
Uromodulin[b]	CKD	Urine	[30]
TIMP-2/IGFBP-7	AKI	Urine	[31]
SDMA[b]	HD, CKD, ESKD	Serum/Plasma	[30, 31]
ADMA[b]			
Albumin/Creatinine ratio[a]	CKD, DN	Urine	[32, 33]
Beta-2 microglobulin	CKD, AKI	Urine	[34]
PAPP-A	RT, HD	Serum	[8, 35]

Standard biomarkers for renal diseases[a], novel biomarkers[b]. BTP, beta-trace protein; KIM-1, kidney injury molecule; NGAL, neutrophil gelatinase–associated lipocalin; TIMP2, tissue inhibitor of metalloproteinase-2; IGFBP-7, insulin like growth factor binding protein 7; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; PAPP-A, pregnancy associated plasma protein A.

PAPP-A

Structure of PAPP-A

PAPP-A is a metalloproteinase and belongs to pappalysins, a member of metzincin superfamily. Metzincin superfamily has four subfamilies known as astacins, serralysins, adamalysins/reprolysins and matrix metalloproteases but PAPP-A shows no global sequence similarity and does not conform of these subfamilies and therefore it is the founding of the 'pappalysins' subfamily (fifth metzincin subfamily) which consists PAPP-A, PAPP-A2 and Ulilysin (an archaeal proteinase) [36]. In circulation of human body PAPP-A exists in two main forms. In pregnancy, two PAPP-A molecules linked to two eosinophil major basic protein molecules (proMPB) and forms 2:2 heterotetrameric complex [37]. Binding proMPB inhibits the catalytic activity of PAPP-A against its all substrates. The active form of PAPP-A is a disulphide-linked homodimer with two identical 200 kDa monomers and does not link to proMBP. Each PAPP-A subunit consists of five domains (Figure 1) and the proteolytic domain which consists approximately 350 amino acids located in the N-terminal side [38].

Synthesis and regulation of PAPP-A

In human, the gene of PAPP-A is located on chromosome 9q33.1 and it consists of 22 exons and 21 introns [37, 38]. Although the cDNA of PAPP-A encodes 1,627 amino acids [39], the active form of PAPP-A has 1,547 amino acids [40]. PAPP-A is synthesized in fibroblasts and osteoblasts [41] and high expression have been detected particularly in bone and kidney [42].

The regulation of PAPP-A has been studied in different tissues. Pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α are the most potent stimulator of PAPP-A expression in human coronary artery smooth muscle cells [43], and dermal fibroblasts [44]. In addition to TNF-α and IL-1β; forskolin, prostaglandin E2, transforming growth factor-β and IL-4 stimulate the expression of PAPP-A in human osteoblast [45]. On the other hand, N-acetyl cysteine [46] and resveratrol [43] decrease the expression of PAPP-A. Although activated macrophages do not directly synthesize PAPP-A, they stimulate the expression of PAPP-A through the secretion of pro-inflammatory cytokines such as IL-1β and TNF-α [47].

Stanniocalcin-1 (STC-1) and stanniocalcin-2 (STC-2) are homologous proteins with re-ported regulatory activity for PAPP-A and STC-2 is expressed in kidney tissue [48]. STC-2 forms a covalent bond with PAPP-A and irreversibly inhibits its proteolytic activity while STC-1 inhibits PAPP-A by forming a high-affinity (Ki=68 pM) non-covalent complex [49].

Function of PAPP-A

Although PAPP-A was discovered in 1974 and used as a biomarker for screening in some genetic testing such as Down's syndrome [50] and Edwards' syndrome [51] its biological functions have not been elucidated for years. In 1999, Lawrence et al. isolated PAPP-A from fibroblasts and demonstrated its IGF dependent IGFBP-4 protease activity [52].

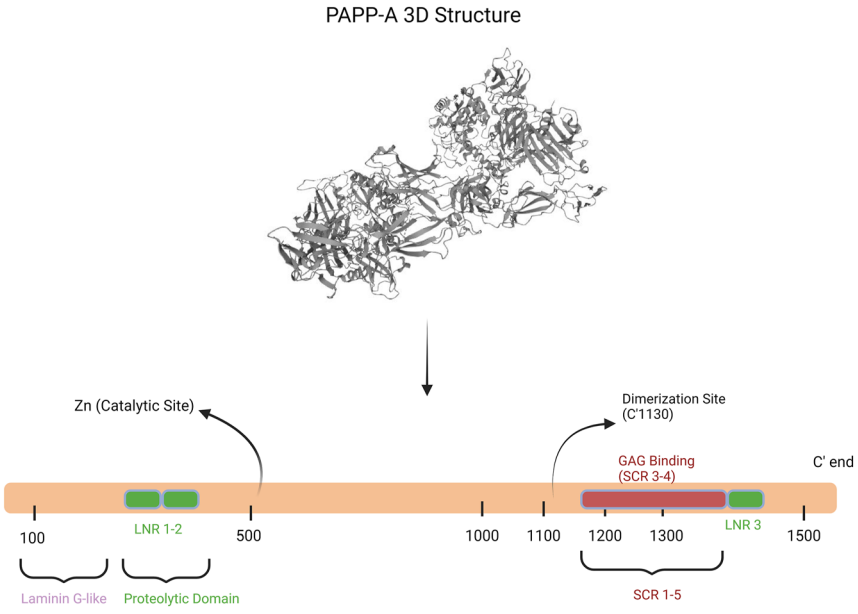

Figure 1: Monomer structure of PAPP-A protein. It consists of four functional regions. These are laminin G-like domain, a proteolytic domain which consists of LNRs, five sequential SCRs and C'end with LNR3. LNR: Lin-notch repeats, it is important in substrate recognition. SCR: short consensus repeats. GAG: glycosaminoglycans, created with BioRender.com, 2023.

The insulin-like growth factor (IGF) signaling pathway is a complex integrated system and regulates the activities of IGFs. It consists of IGF I and II, six IGF binding proteins (IGFBP 1–6), IGFBP proteases and IGF receptors. IGFBPs bind IGFs and inhibit their activity and therefore degradation of IGFBPs results elevated level of bioavailable IGFs. Due to the proteolytic activity on IGFBPs, PAPP-A has a central role in IGF signaling pathway. The proteolytic activity of PAPP-A is not limited to IGFBP-4, it also catalyzes the degradation of IGFBP-2 and IGFBP-5 [38].

IGFBP-4 can bind IGF-I and IGF-II ligands with high affinity and prevents the interacting with cell surface IGF receptors. PAPP-A degrades IGFBP-4, releases IGF into the pericellular environment, which binds to IGF-I receptor (IGF-IR) and stimulate cell growth and cell survival signals [38] (Figure 2).

Measurement of PAPP-A

Numerous studies show the measurement of PAPP-A. The PAPP-A test reported a limit of detection (LOD) of 4 mIU/L. The mean normal value in healthy persons has been discovered to be 10 mIU/L, while 95 % of individuals had PAPP-A concentrations less than 14 mIU/L. These results were acquired utilizing the KRYPTOR analyzer (BRAHMS GmbH, Henningsdorf, Germany) and the TRACE (time resolved amplified cryptate emission) approach, which included two anti-PAPP-A monoclonal antibodies. Differences in PAPP-A measurements between research are due to variations in the analytic methodologies utilized [53].

Reference interval, biological variation and reference change value of PAPP-A

Reference interval (RI), biological variation (BV) and reference change value (RCV) of biomarkers are essential parameters for the correct interpretation of measurement results. While RIs are commonly used for the diagnosis of diseases, RCV is preferred in the monitoring of patients. For the first time Coskun and his colleagues measured the RI [54] and BV of PAPP-A and calculated its RCV [55]. Accordingly, the BV of PAPP-A was 12.6 % and RCV was 30.0 ($p<0.5$), therefore PAPP-A has a moderate individuality and should be considered in the evaluation of clinical outcomes.

PAPP-A in renal diseases

As mentioned previously, PAPP-A is expressed in high level in several kidney diseases and therefore has been proposed as a biomarker for various kidney diseases as reviewed below. Serum levels of PAPP-A in patients with and without Kidney Diseases is summarized in Table 2.

Acute kidney injury

The incidence of AKI increases in critically ill patients with advanced cardiovascular, infectious, endocrine, respiratory diseases, and poisoning [69]. AKI affects hospitalized patients at rates ranging from 5 to 30 % [70], and this rate rises approximately to 60 % in patients admitted to the intensive care unit [71]. It refers to the rapid decline of kidney function

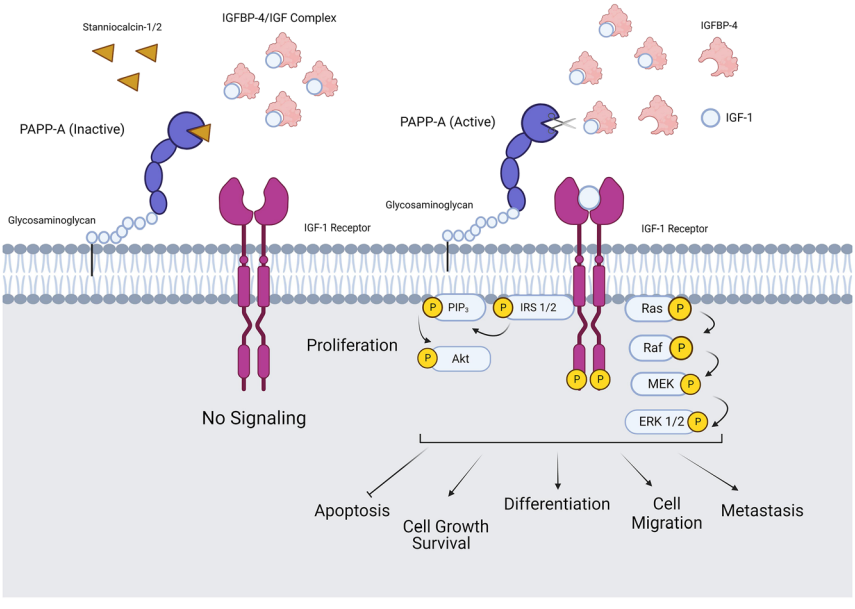

Figure 2: Mechanism of IGF signaling and the role of PAPP-A. PAPP-A is a secretory enzyme that connects with heparin-like proteoglycans by using the 3rd and 4th of the 5 C-terminal consensus repeats in secretory and adjacent cells. PAPP-A cleaves IGFBP-4 in an IGF-IGFBP-4 complex/significantly reduces IGFBP-4's affinity for IGF, while PAPP-A-STC complex, prevents PAPP-A to cleave the IGFBP-4 (PAPP-A is inactive). IGF is released into the pericellular environment, facilitating receptor binding. IGF binding initiates specific IGF-1 receptor signal transduction via AKT or RAS/ERK to mediate cell growth survival, differentiation, cell migration and metastasis. Also, this signaling can block apoptosis. Created with BioRender.com, 2022.

Table 2: Serum levels of PAPP-A in patients with and without kidney disease.

Disease	n	Patient, mIU/L	n	Control, mIU/L	p-Value	Method[e]	Ref.
AKI	40	20.0 ± 16.9	39	9.1 ± 2.3	<0.001	TRACE	[56]
CKD	42	20.2 ± 28.1	39	9.1 ± 2.3	<0.001	TRACE	[56]
	159	12.1 ± 8.5	44	9.3 ± 2.2	0.001	TRACE	[57]
	20	153.16 ± 70.425[a]	20	6.291 ± 2.807[a]	<0.001	ELISA	[11]
DN	178	3.7 (2.0–5.9)	152	2.4 (1.0–4.6)	<0.001	Biotin immunoassay	[58]
	197	3.6 (0.4–51.1)[c]	178	2.2 (0.4–46.6)[c]	<0.001	Biotin immunoassay	[59]
HD	31	20.8 ± 10.1	39	9.1 ± 2.3	<0.001	TRACE	[56]
	36	27.0 ± 16.5	25	8.22 ± 2.7	<0.001	TRACE	[60]
	261	27.6 ± 15.5	61	9.4 ± 2.5	<0.001	TRACE	[61]
	319	25.6 ± 14.3	145	9.3 ± 2.4	<0.001	TRACE	[62]
	99	4.7 (3.8–6.5)	41	3.4 (3.0–5.0)	<0.05	ELISA	[63]
	65	15.2 (<0.03–158.8)[b,c]	26	6.2 (<0.03–16.4)[b,c]	<0.01	ELISA	[64]
	29	26.23 ± 11.94	16	11.41 ± 1.94	<0.001	TRACE	[65]
	40	5.8 (5.1–11.6)	30	5.1 (4.1–6.7)	0.005	ECLIA	[66]
PD	10	14.07 ± 6.73	25	8.22 ± 2.7	<0.001	TRACE	[60]
	14	4.5 (3.2–6.7)	41	3.4 (3.0–5.0)	<0.05	ELISA	[63]
RT	78	10.5 (6.4–15.4)	37	3.9 (3.1–5.2)	<0.001	ELISA	[9]
	178	1.14 (0.19–12.86)[c]	40	0.96 (0.16–3.08)[c]	0.057	ELISA	[67]
RCC	121	8.74 ± 3.5	69	8.24 ± 2.3	0.24	TRACE	[68]

Data are mean ± SD, or median (25th percentile – 75th percentile). [a]pg/mL. [b]ng/mL. [c] Median (range). [d] Median (rank). [e]The patient and control group of this study consisted of children. TRACE, time resolved amplified cryptate emission, ELISA, enzyme-linked immunosorbent assay; ECLIA, electro-chemiluminescence immunoassay. [f]A variety of assays can be used to measure PAPP-A, each with different analytical properties and limitations. Although this review is not intended to compare the analytical performance of different measurement methods, it is important to recognize that differences in PAPP-A, measurements across studies may be due to methodological differences, which may be related to the type of assay used or whether total or complex PAPP-A, levels are measured.

accompanied by an increase in serum creatinine and dereease in urine output in a short period of hours, days [72]. Prolonged disease may be diagnosed as Acute Kidney Disease (AKD), CKD or ESKD depending on the existing damage and duration [17]. According to KDIGO, increasing serum creatinine concentration 0.3 mg/dL in 48 h or a period of 6 h during which urine output is less than 0.5 mL/kg/h indicates the presence of AKI [72]. The first 48 h are critical for treatment, but serum creatinine and urine output do not provide adequate information about the onset [73]. Besides, serum creatinine is affected by many factors such as age, nutrition, infection status and cannot adequately reflect kidney damage; especially in early diagnosis [74]. Furthermore, in the monitoring of AKI, serum creatinine is widely used to evaluate the GFR, but its sensitivity and specificity is not at the desirable level. On the other hand, while KIM-1 has 74 % sensitivity and 86 % specificity [75]; NGAL has 93 % sensitivity 98 % specificity for predicting AKI [76]. Direct detection of kidney damage still requires biopsy [77]. Although continued use of serum creatinine and urine output is recommended, there is consensus that biomarkers are needed for diagnosis of disease and early detection of damage [73].

Novel biomarkers such as TIMP-2/GFBP7 [31], NGAL [78], KIM-1 [7] and cystatin C [25] have potential clinical use of management of AKI and continue to be investigated, particularly to detect kidney damage before GFR is decreased [79]. The combination of TIMP-2/IGFBP7 urinary levels has been found to be useful in predicting AKI and monitoring recovery [80]. It has also been reported that TIMP-2/IGFBP7 levels increase independently in the presence of diabetes [81]. An elevated serum level of cystatin C reflecting AKI can be detected several days before a notable rise in serum creatinine [82]. In comparison to creatinine, Cystatine C has potential advantages and less effected by sex and muscle mass, but long laboratory turnaround time and low specificity seems the main disadvantages of Cystatine C [80, 81]. It has been suggested that KIM-1 can detect different stages of kidney damage and this distinction is critical given the rapidly progressing nature of AKI [83]. KIM-1 may be elevated in chronic proteinuria and inflammatory conditions, and its high cost and low availability are difficulties encountered in clinical use [76, 84]. NGAL might be elevated in sepsis, CKD and infection also it doesn't have specific cutoff values [76, 83]. The need of more sensitive and specific biomarkers for the management of AKI stands an urgent requirement.

PAPP-A may have potential use for AKI due to its association with various kidney diseases, which will be detailed

in the following sections. However, it has not been evaluated in detail in the management of AKI. According to Zakiyanov et al., the only available study measuring PAPP-A in AKI, indicates that serum PAPP-A levels are significantly elevated in AKI patients (as shown in Table 2). In addition, PAPP-A correlated positively with transferrin and negatively with albumin, but not with C-reactive protein (CRP) in AKI patients [56]. Based on only one study we cannot make a conclusion about the clinical significance of PAPP-A in the management of AKI and further studies are need for the confirmation. Studies including and co-evaluating PAPP-A with other potential AKI biomarkers mentioned above would be beneficial for the assessment of PAPP-A as a biomarker in AKI.

Chronic kidney disease

Chronic kidney disease affects more than 800 million people worldwide [85] and can generally be defined as abnormal kidney function or GFR <60 mL/min/1.74 m^2 over a 3-month period. According to National Kidney Foundation, CKD is stratified into different stages with increasing the severity of disease from stage 1 (kidney damage with normal or elevated GFR) to Stage 5 (GFR is <15 mL/min/1.73 m2) [86]. CKD can develop because of various reasons including diabetes mellitus, hypertension, glomerulonephritis, hereditary diseases, obstructive conditions, and unknown reasons [87]. Identifying the underlying cause is critical from diagnosis to treatment. KDIGO 2024 emphasizes that the significance of biomarkers in CKD diagnosis and monitoring [6]. Serum creatinine, cystatin C and urine albumin to creatinine ratio reflect the status of chronic kidney disease [88] but have not been useful in screening asymptomatic patients [89]. It is possible to detect pathological changes with kidney biopsy, but the fact that it is an invasive method limits its use, especially for pre-screening and follow-up purposes [90].

ADMA and its enantiomer SDMA have been proposed as a biomarker due to their elevated levels in CKD. Since these molecules are identified as independent risk factors for cardiovascular diseases, they may be elevated outside of kidney damage [91]. As another novel biomarker, uromodulin has been suggested to have the potential to detect early stages of CKD by assessing tubular function [4]. Since ADMA, SDMA, and uromodulin are currently insufficient as standalone CKD biomarkers, the combined use of several biomarkers has come to the fore [92]. The progressive nature of CKD highlights the importance of clinically suitable biomarkers for diagnosis and follow-up, especially from the early stages of the disease. As can be followed below, PAPP-A is one of the potential biomarkers evaluated for CKD.

Zakiyanov et al. measured serum PAPP-A levels in CKD patients (stage 5) and age-matched healthy control subjects and in comparison, to control group they reported significantly elevated level of PAPP-A in CKD patients [56]. Mohammed et al. [11] measured serum PAPP-A levels in 5–15 years of children (10.4 ± 3.2 years) with at least 6 months of CKD receiving hemodialysis (22.9 ± 16.5 months) and reported significantly higher levels in CKD patients compared with the control group. The authors reported that, at a 2-year follow-up, 60 % of CKD patients developed cardiovascular disease. For a cutoff point of ≥154.4 pg/mL, the sensitivity and specificity of PAPP-A for predicting cardiovascular outcomes in CKD patients were reported as 75 and 87.5 %, respectively [11]. The aforementioned studies reported the significantly elevated levels of PAPP-A in CKD patients, but they did not evaluate the diagnostic power of serum PAPP-A to predict the presence or the stages of CKD. On the other hand, Li et al., meta-analysed the data of 2034 subjects from 6 studies and concluded that, elevated serum PAPP-A level is a risk factor for the mortality in CKD patients [93].

Dialysis and transplantation

The number of patients in need of dialysis or kidney transplant worldwide has been reported as 9.7 million and is estimated to reach 14.5 million in 2030 [18]. Morbidity and mortality rates are closely related to access to treatment. Although dialysis and transplantation are critical in the management of ESKD, the quality of life of the patients is low and they require lifelong follow-up. Dialysis can be one of the HD or PD methods, one is not superior to the other in the long-term treatment focus, and subclinical inflammation and increased oxidative stress are common [94]. Acute or chronic rejection and cardiovascular complications that may develop after kidney transplantation pose a problem [95]. Today, traditional methods such as GFR and proteinuria measurements and renal allograft biopsy continue to be used in the follow-up after kidney transplantation [96]. At the initial stage of kidney damage or rejection, biopsy is insufficient when histological changes are not evident [95]. NGAL and TIPM-2, which are generally studied for AKI, have also been found useful for kidney transplant patients as they have the potential to predict delayed graft function [95, 96]. Except these, albumin/creatinine ratio which should normally be less than 30 mg/g creatinine [6], is mostly used in the detection of albuminuria to predict kidney function. At cut-off value of 30 mg/g, the sensitivity and specificity were reported as 60 and 97 %, in men, and 46 and 95 % in women, respectively [97].

In recent years, search for biomarkers that can be used in dialysis patients and kidney transplant follow-up, have been carried out comprehensively based on genomic, proteomic and transcriptomic studies [98]. However, there is currently no specific marker available for clinical use based on these studies. A new monitoring tool remains necessary in both dialysis and renal transplant patients.

PAPP-A, has been also suggested for the evaluation of dialysis and renal transplant patients. Kalousová et al. measured serum PAPP-A level in 40 HD patients and followed-up the study group for 20 months. 22 patients died and most of them (15 patients) from cardiovascular diseases during the follow-up period. The authors found higher median PAPP-A level 26.8 mU/L in patients who died than those living 20.0 mU/L, $p<0.05$ and concluded that PAPP-A could be a prognostic biomarker especially in HD patients with cardiovascular events [99].

PAPP-A levels have been reported to be transiently elevated during HD sessions [100]. Our group measured serum PAPP-A level in HD and PD patients and in comparison, to healthy subjects we found significantly elevated level of PAPP-A in all dialysis patients. Within the same study, an increase in PAPP-A levels was detected after the dialysis procedure (median duration 24 months) in HD patients [63]. Laskowska et al. [101] found no difference between PAPP-A levels according to the duration (more or less than 60 months) of hemodialysis. Fialová et al. [60] measured serum PAPP-A level in both HD and PD patients and found elevated PAPP-A levels in both groups of dialyzed patients in comparison to healthy participants. In HD patients a significant correlation was observed between serum PAPP-A and CRP ($r=0.48$, $p<0.05$), but no correlation was found with serum creatinine. They also found that PAPP-A levels were significantly higher in HD than in PD [60]. On the contrary, our group did not detect any significant difference between PD and HD patients [63].

Our group also evaluated the potential of PAPP-A as a prognostic marker for HD and examined its relationship with intact parathormone (iPTH), phosphorus and bicarbonate levels. We found significantly higher PAPP-A level in HD than control subjects and additionally PAPP-A was negatively correlated with bicarbonate ($r=-0.291$; $p<0.01$) but positively with phosphorus ($r=0.230$; $p<0.05$) and iPTH levels ($r=0.273$; $p<0.01$) in HD patients [64]. Metabolic acidosis is a well common complication of kidney damage and has been associated with uremic bone diseases [102]. Elevated level of PAPP-A and its association with bicarbonate and uremic bone diseases parameters suggest that PAPP-A may be a prognostic factor for patients undergoing dialysis however this needs to be further investigated.

Nilsson et al. measured plasma PAPP-A level in 286 dialysis patients and participants were followed up until transplantation, death or end of study (60 months). The authors found association between PAPP-A level and high-sensitivity C-reactive protein, moreover they concluded that elevated level of PAPP-A is a risk factor for mortality in HD patients with accompanying diabetes [103].

Serum PAPP-A levels above 24 mIU/L were defined as high-risk category. The probability of survival at the end of the observation period was calculated as 91 % for patients with PAPP-A levels below 24 mIU/L [104].

According to a prospective cohort study, PAPP-A levels were elevated in HD patients and correlated with creatinine. Within the same study, based on multivariate Cox analysis authors proposed PAPP-A as an independent predictor for overall mortality in HD [61].

Studies of PAPP-A in renal transplant patients are very limited. Our group found higher PAPP-A levels in renal transplant patients in comparison to the control group and significant positive correlation was observed with urea, creatinine, uric acid and CRP [9]. Another study reported a decrease after transplant, but still higher than in healthy individuals. PAPP-A has been positively correlated with CRP, IL-6 and TNF-α and has been suggested as a predictor for post-transplant cardiovascular events and chronic allograft nephropathy [67].

Current studies have shown that serum PAPP-A levels are high in dialysis patients, also highlight its potential to predict survival. More studies are needed to evaluate the potential of PAPP-A as a biomarker in renal transplant patients.

Diabetic nephropathy (DN)

Diabetes mellitus is a metabolic disorder based on impaired insulin hormone action and/or secretion [105]. According to International Diabetes Federation (IDF) Diabetes Atlas, the estimated number of diabetic patients worldwide is reported as 537 million, and diabetes mellitus is the cause of 6.7 million deaths (age: 20–79 years) in 2021 [106].

DN is the most common complication of diabetes mellitus and affects at least 30 % of diabetic patients [107]. It occurs as a result of microvascular lesions in the kidney glomerulus. Increasing evidence over the past two decades shows that hyper-glycemia mediates its effects on vasculature and contributes to the development of DN [105]. Progressive structural and functional changes such as thickness of the glomerular basement membrane (GBM), enlargement of Bowman's capsule, enlargement and nodule formation in

the mesangial matrix, and deterioration in podocytes eventually impair glomerular filtration are accompanied with DN [108].

Albumin is prevented from leaking into the urine by the glomerular filtration barrier [109]. The presence of a modest amount of albumin (30–300 mg/day) in the urine is considered as the first identifiable sign of DN [110]. Nevertheless, albumin can be detected within this range even in the absence of kidney damage. When the albumin level is severely increased (>300 mg/day) and the eGFR decreased below the normal limits (<90 mL/min per 1.73 m2) irreversible loss of kidney function has already occurred [111]. Therefore, albumin and eGFR are insufficient as prognostic tools in the early stages of the disease [112].

As in CKD, the progressive nature of the DN emphasizes the importance of early diagnosis. Several biomarkers identified for AKI have been proposed in DN assessments, but their usefulness is debated [113]. IGFs has been associated with DN pathology [114].

It has been suggested that stimulation of human mesangial cells with IGF-1 leads to the development of DN due to structural changes in mesangial cells and impaired glomerular function [115]. Elevated levels of IGFBP-4 have been reported in DN patients and correlates positively with albumin and negatively with EGFR, consistent with DN pathology [116]. Moreover, several studies have been evaluated the role of PAPP-A in DN, as can be followed below.

Hjorteberg et al. compared patients with persistent normoalbuminuria and patients with diabetic nephropathy and found significantly elevated IGF-1, IGF-2, IGFBP-4, proMBP and PAPP-A levels in patients with diabetic nephropathy [58]. Astrup et al. have found plasma levels of PAPP-A were much higher in patients with diabetic nephropathy 3.6 (0.4–51.1) mIU/L [median (range)] than normoalbuminuric patients 2.1 (0.4–46.6) mIU/L ($p<0.001$). It has been reported that PAPP-A associated with increased cardiovascular risk and PAPP-A is also useful in predicting all-cause mortality in type 1 diabetic patients [59]. According to the findings of a study conducted by Mader et al., PAPP-A expression was significantly increased in the glomerulus of human diabetic kidneys [117]. Affirmatively, Jepsen et al. also reported increased glomerular PAPP-A expression level in DN [118].

In kidneys of mice with targeted PAPP-A gene deletion, the incidence of pathological changes indicative of the presence of nephropathy, including basement membrane thickening, glomerulosclerosis, and tubular dilatation, is reduced compared to wild-type mice [119].

In order to evaluate the potential role of PAPP-A in the development of DN, the kidney histopathology of wild-type and PAPP-A knock out mice with confirmed stable hyperglycemia (for 4 months) was evaluated by Mader et al. Accordingly, bowman's capsule thickening was detected in the kidneys of all diabetic wild-type mice, and an increase in glomerular size in 80 % of the mice. Otherwise, PAPP-A deficient mice showed no change in the same parameters and they were resistant to the development of DN [117].

In a study by Donegan et al., [120] it was found for the first time that PAPP-A is expressed and produced in normal human mesangial cells and it's regulated by proinflammatory cytokines. Also, they showed that PAPP-A produced by human mesangial cells can serve to increase the local bioavailability of IGF-1 within the glomerulus. Therefore, PAPP-A may represent a new therapeutic target in inflammatory conditions of the glomerulus in patients with DN.

A recent study has shown that PAPPA, which exhibits high levels in DN, does not form a complex with STCs and thus exists in its active form. In the same study, inhibition of PAPP-A by conditional overexpression of STC-2 was shown to cause a reduction in glomerular growth in diabetic mice [118]. In the light of all these studies, the idea that PAPP-A has an effect on DN pathology is strengthened. Inhibition of PAPP-A has the potential to prevent the development of DN.

Polycystic kidney disease (PKD)

PKD is characterized by substantial kidney enlargement due to progression of epithelial lined cysts derived from renal tubules [121] and is the underlying cause of about 10 % of ESKD cases [122]. The most common genetic renal disorder: autosomal dominant form of PKD develops as a result of mutation in genes which encodes polycystins PC1 and PC2. Mutations that cause disruption or complete loss of function in polycystins play a role in cyst formation, while epithelial cell hyperproliferation causes their enlargement. Multiple and progressive cysts compress and damage surrounding tissues; and causes fibrosis, inflammation and often complete loss of kidney function [123].

To date, several studies have shown that IGF axis is involved in PKD and may also play a role in the progression of cystic lesions [124]. A recent study conducted by Kashyap et al. specifically emphasizes that PAPP-A has a central and important role in the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). In the comprehensive study, different tissues of ADPKD mouse models such as kidney, brain, lung, heart, liver were compared with WT mice to determine PAPP-A mRNA expression level. PAPP-A was observed to be up-regulated only in the kidney. In the same study, PAPP-A levels in cystic fluids of patients with ADPKD were measured 9 times higher than serum and PAPP-A expression in cystic epithelial cells derived from ADPKD

patients was higher than in normal human kidney cortical tubular epithelial cells. They also found that the expression of PAPP-A in same murine models was positively regulated by the cAMP/CREB/CBP/p300 pathway. Moreover, in the ADPKD mouse model, genetic deletion of PAPP-A resulted in a considerable reduction in cyst growth and a significant improvement in inflammation, renal damage, and fibrosis. In addition, improvement in glomerular filtration rate and survival was observed [125].

This study in 2020 indicates the direct involvement of PAPP-A in ADPKD and the requirement for additional extensive research.

Kidney cancer

According to the latest report of GLOBOCAN, kidney cancer constitutes approximately 5 % of cancers, with more than 430,000 new cases in 2022 [126]. Around 90 % of kidney malignancies are renal cell carcinomas (RCC), which are tumors originating from the renal epithelium [127].

Recent studies have drawn attention to the relationship between dialysis [128], renal transplant [129], CKD [130] and RCC, beyond which ESKD is already considered a risk factor for RCC [131].

Several distinct histological subtypes of RCC have been defined according to the WHO classification; Clear cell renal cell carcinomas (ccRCC), papillary renal cell carcinomas (pRCC), and chromophobe renal cell carcinomas (crRCC) [132]. Clear cell renal carcinoma (ccRCC) constitutes 75 % of renal cell carcinoma cases, it is followed by papillary renal cell carcinoma responsible for about 15 % [127].

Von Hippel-Lindau (VHL) gene known as tumor suppressor is generally mutated in many types of cancer especially common in ccRCC [133]. Mutated VHL causes uncontrolled expression of Hypoxia-inducible factor (HIF) target genes and vascular endothelial growth factor (VEGF). Hypoxia-inducible factor-alpha (HIF) is a transcription factor which is significant in hypoxia and cancer development [134]. It has been shown that HIF-1alpha is induced in response to IGF-1 [135] and suppression of IGF-I downregulates HIF-1alpha and VEGF expression [136].

Members of the IGF family, including PAPP-A have been associated with different cancers such as lung [137], ovarian [138], and kidney [139].

The proteolytic role of PAPP-A in IGF signaling mediates the observation of the effects by suppressing physiological and pathological activity of IGF in PAPP-A knock-out mouse models. They are small in size like IGF-2 knockout mice in the neonatal and postnatal stage and show delayed skeletal development [42] and decreased severity of cardiomyopathy, nephropathy, neurodegenerative lesions [119]. Furthermore, dysfunction of IGF signaling and elevated PAPP-A expression levels have been found associated with different types of cancer such as breast, and lung cancer [140].

A limited number of studies examining PAPP-A in RCC are as follows; Cechova et al. compared serum PAPP-A levels in patients with ccRCC (n=121) and healthy subjects (n=69) to evaluate the utility of PAPP-A in both diagnosis and follow-up. According to their findings, PAPP-A serum levels in ccRCC patients before or after nephrectomy reflect no significant difference compared to healthy individuals [68].

Lu et al. conducted a study involving several methods to elucidate the role of PAPP-A in RCC [141]. They initially performed transcriptional sequencing analysis and compared PAPP-A mRNA expression levels in ccRCC tissue (n=10) and healthy kidney tissue (n=10). Afterwards, PAPP-A mRNA levels using real-time qPCR (n=29) and PAPP-A protein levels using western blot analysis (n=13) were compared between an equal number of ccRCC and normal tissue. Finally, statistical analysis was performed with data from the TCGA database to compare PAPP-A expression levels in ccRCC (n=72) and paracarcinoma tissues (n=72). Based on transcriptional sequencing analysis, qPCR, western blot and statistical analysis of TCGA data, PAPP-A levels were significantly lower in ccRCC. It was also stated that the detected decrease was not affected by the stage of ccRCC or the lymph node metastasis status [141].

Studies evaluating PAPP-A in renal cancer are limited to the ccRCC subtypes. Similar PAPP-A trend was not observed in ccRCC compared to its increased values in various cancer types including lung, ovarian, breast and ewing sarcoma. Further studies are needed to elucidate the mechanisms underlying the decreased values of PAPP-A detected in ccRCC and to evaluate its significance in different subtypes of kidney cancer.

Conclusions

Despite the limitations of biomarkers in use and significant advances in knowledge of molecular and cell signaling pathways involved in kidney diseases, an unmet need for an early detection tool remains. In this context, we examined PAPP-A as a novel biomarker candidate for kidney diseases.

Based on current research, several findings from different studies that we discussed in the earlier sections highlighted the reducing or inhibitory effect of PAPP-A on the development of diabetic nephropathy pathology. In addition, although there is a potential of PAPP-A as a biomarker in ESKD due to elevated PAPP-A serum levels detected in dialysis and renal transplant patients, the reason of this elevation needs to be determined. While expression of PAPP-A is increases in lung,

ovarian and, breast cancer, its low or insignificant expression in RCC indicates two different results. Elucidating the mechanism underlying these results may contribute to clarify the role of PAPP-A in cancer development.

Targeting PAPP-A with various molecules known to reduce PAPP-A expression, such as N-acetyl cysteine or Resveratrol, or STC-1 and STC-2 homologous proteins that inhibit PAPP-A activity may pave the way for a therapeutic approach to kidney diseases.

As a result of this review, we have found that PAPP-A might be useful for the early diagnosis of diabetic nephropathy and chronic kidney disease. However, comparative analyses including traditional biomarkers such as serum creatinine and microalbumin are required to assess PAPP-A's potential in the early identification of kidney diseases. Further studies are needed to focus on its effectiveness.

Acknowledgments: We would like to thank Prof. Dr. Abdurrahman Coşkun for his valuable guidance and support throughout the preparation of this manuscript. We also thank all colleagues who provided encouragement during the writing process.

Research ethics: Not applicable. This study is a narrative review article and did not involve human or animal subjects.

Informed consent: Not applicable.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Use of Large Language Models, AI and Machine Learning Tools: None declared.

Conflict of interest: The authors state no conflict of interest.

Research funding: None declared.

Data availability: Not applicable. This review is based on previously published studies, all of which are cited in the reference list.

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