Ann. Acad. Med. Siles. (online) 2017; 71: 265–274
eISSN 1734-025X
DOI:10.18794/aams/65841

PRACA POGLĄDOWA
REVIEW

The role of suPAR in kidney diseases

Rola suPAR w chorobach nerek

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ABSTRACT

Chronic kidney disease (CKD) is unquestionably a problem of social significance because it affects about 10% of the population. There is a search for biomarkers which could help select persons out of such a large group of patients with a high risk of disease progression and of its complications. The major cause of death in patients with end-stage renal disease are cardiovascular diseases. Accelerated atherosclerosis in this group of patients is associated with a chronic inflammatory state. The new biological marker of inflammation suPAR (soluble urokinase-type plasminogen activator receptor), is the focus of attention of the authors of this report. The relationship of suPAR with urinary tract infections and focal segmental glomerulosclerosis is also very interesting from the clinical perspective. The perception of suPAR as a blood circulating factor, inducing FSGS, throws new light on the pathomechanism of this medical condition, while unveiling promising therapeutic perspectives. A better understanding of the pathogenesis of the diseases discussed will help to reduce the unacceptably high mortality rate in patients with CKD. At present, common assaying of suPAR is not yet possible in the context of the above-mentioned issues. Nevertheless, studies are ongoing which may explain the still unclear issues concerning the relationship of the biomarker with the mentioned kidney diseases. Perhaps, following their results suPAR assays may in the near future become routine diagnostics means in selected kidney diseases.

KEY WORDS
chronic kidney disease, cardiovascular disease, suPAR, FSGS

STRESZCZENIE

Przewlekła choroba nerek (PChN) to niewątpliwie problem o znaczeniu społecznym, dotyczy bowiem około 10% populacji. Poszukiwane są biomarkery, dzięki którym spośród tak dużej liczby pacjentów udałoby się wyselekcjonować osoby z dużym ryzykiem progresji choroby i jej powikłań. Główną przyczyną zgonów u pacjentów ze schyłkową niewydolnością nerek są choroby układu sercowo-naczyniowego. Przyspieszony rozwój miażdżycy w tej grupie chorych wiąże się z przewlekłym stanem zapalnym. Przedmiotem zainteresowania autorów pracy jest nowy biomarker

Received: 15.06.2016 **Revised:** 30.08.2016 **Accepted:** 15.10.2016 **Published online:** 01.08.2017

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stanu zapalnego suPAR (*soluble urokinase-type plazminogen activator receptor* – rozpuszczalna forma receptora aktywatora plazminogenu typu urokinazy). Z klinicznego punktu widzenia interesujący jest również związek suPAR z zakażeniami układu moczowego oraz ogniskowym segmentalnym stwardnieniem kłębuszków nerkowych (*focal segmental glomerulosclerosis* – FSGS). Identyfikacja suPAR, jako krążącego we krwi czynnika wywołującego FSGS, rzuca nowe światło na patomechanizm choroby i stwarza obiecujące możliwości lecznicze. Lepsze zrozumienie patogenezy omawianych schorzeń pomogłoby zredukować nieakceptowalnie wysoką śmiertelność pacjentów z PChN. Na dzień dzisiejszy nie można zlecać powszechnego oznaczania suPAR w kontekście omawianych zagadnień. Niemniej trwają badania, które pozwolą wyjaśnić niejasne kwestie dotyczące związku biomarkera z omawianymi schorzeniami nerek. Być może na podstawie ich wyników w najbliższych latach oznaczanie suPAR w wybranych chorobach nerek będzie rutynowe.

SŁOWA KLUCZOWE

przewlekła choroba nerek, choroby układu sercowo-naczyniowego, suPAR, FSGS

INTRODUCTION

Chronic kidney disease (CKD) is a multisymptomatic syndrome which develops as a result of a decreasing number of active nephrons in the course of disease processes in renal parenchyma. Regardless of all the differences in latitude, race, climate, habits and customs, the incidence of chronic kidney disease is everywhere estimated at least 10% of the population. It certainly concerns various stages of the disease progression. CKD is unquestionably a disease of social significance as it affects more than 600 million people worldwide (4 million people in Poland alone) [1]. A report from the status of renal replacement therapy implementation in Poland published in 2012 and covering the time period of the year 2009, states that in the population of patients with end-stage renal disease, renal replacement therapy was initiated in a total of 5124 subjects, which provides an incidence rate of 134 per million of the population. Altogether, 21,092 patients with chronic kidney disease were dialysed in 2009, out of which number 2980 dialysed patients, i.e. 18% died. The deaths were most often associated with cardiovascular conditions, with a mortality rate amounting to 58%. Bacterial infections ranked second (approximately 12.4%) and neoplasms were third (8.3%) [2]. Such a large population of patients cannot, for many reasons including economic, be a target of complex medical care. What is more, the commonly used markers of renal dysfunction (creatinine, urea, albuminuria) are not ideal. Therefore, a continuous search for new markers is ongoing, with the primary goal to find such markers which would allow the identification of patients with CKD with a high risk of disease progression and its complications. By implementing appropriate diagnostic protocols and therapeutic management, it could perhaps be possible to reduce morbidity and especially, mortality in this group of patients.

Taking into account the results of studies from recent years, it seems that the soluble urokinase-type plasminogen activator receptor (suPAR) could be a new, promising determinant of CKD progression and its complications.

AIM OF STUDY

An attempt was made to find an answer to the question, if – in the light of current studies – suPAR could be a marker, useful in everyday clinical practice in the context of three issues: cardiovascular diseases in patients with chronic kidney disease, infections of the urinary tract and focal segmental glomerulosclerosis (FSGS). The presented studies throw new light, even on the pathomechanism of FSGS or the mechanism of fibrinolysis activation in patients with CKD. However, many issues still remain unclear. Further studies are necessary to explain in detail disputable issues concerning suPAR association with the discussed issues.

What is suPAR?

suPAR is the soluble form of the urokinase-type plasminogen activator receptor (uPAR), one of the components of the fibrinolytic system. It was identified by Ploug et al. in 1991 [3]. Since that time, intensive studies have been continued on its biological function. Plasmin is the main enzyme of the fibrinolytic system and originates from plasminogen, an inactive enzyme, under effect of the tissue plasminogen activator (t-PA) and the urokinase-type plasminogen activator (u-PA). t-PA is produced mainly in vascular cells, while u-PA is formed in various cells and organs, including the kidneys. The process of plasminogen transformation into plasmin is inhibited by inhibitors of plasminogen activators: type I (PAI-1), type II (PAI-2) and type III (PAI-3). Alpha2-antiplasmin is the main plasmatic

inhibitor of plasmin. Plasmin, which is formed with participation of the tissue plasminogen activator (t-PA), plays an important role, first of all in fibrin solving, thus in consequence, maintaining of blood vessel patency. In turn, plasmin, produced with the participation of u-PA (urokinase plasminogen activator), brings about activation of pro-metalloproteinases of the extracellular matrix, which degrade matrix components. Thus they play a role in the reconstruction of tissues and migration of cells. Urokinase (u-PA) takes part in converting plasminogen into plasmin, supported by its binding with the specific urokinase-type plasminogen activator receptor (u-PAR) [4,5].

The urokinase receptor (uPAR) is an extracellular glycoprotein, consisting of three homologous domains (DI, DII, DIII). It is connected with the cellular membrane via the glycosylphosphatidylinositol (GPI) chain [3]. It has been proven that this receptor not only binds with urokinase (via DI domain) but also – via DII and DIII domains – with integrins, including beta 3 integrin, high molecular kininogen, and with vitronectin, an extracellular matrix protein [5]. This receptor undergoes expression on the surface of cells which participate in immunological reactions (neutrophils, monocytes, macrophages, activated T-lymphocytes), as well as on the surface of endothelial cells, keratinocytes, fibroblasts, myocytes, megakaryocytes, neoplastic cells and podocytes [3,6]. As a result of an inflammatory status and in effect of the activity of various enzymes, among others, phospholypase, chymotrypsin or urokinase, uPAR may be ”cut off” from the cell surface [7,8,9]. This obstruction is observed either between the GPI chain and DIII domain or between DI and DII domains [3]. As a result, suPAR – a soluble receptor form is produced.

suPAR occurs in three subtypes, depending on the possessed domains: suPAR I-III, suPAR II-III and suPAR I. Their roles are not fully explained, nevertheless, it has been found that suPAR I-III, having a DI domain, maintains the ability to bind with uPA (urokinase plasminogen activator). In the case of subtype II-III, its chemotactic activity has been documented. Numerous studies prove the participation of suPAR in immunological processes: cellular adhesion, migration or chemotaxis [3].

The soluble form of uPAR (suPAR) is present not only in serum or plasma but also, not less significant, in other systemic fluids such as urine, saliva or the cerebrospinal fluid [10,11,12,13].

suPAR is a non-specific marker of the inflammatory status. In particular patients, it reflects the degree of immune system activation. In other words, enhanced activity of the immune system leads to increased suPAR levels. Among others, it is observed in various types of neoplasms, viral or bacterial infections [14,15,16,17,18]. Increased suPAR values are also observed in sepsis and in systemic inflammatory response syndrome (SIRS). While demonstrating little diagnostic significance in sepsis, SIRS or in bacteremias as a single biological marker, it has a higher value in prognosing mortality in these conditions vs. other commonly used markers including C-reactive protein (CRP) and procalcitonin [19,20].

In their study published in 2010, J. Eugen-Olsen et al. [21] demonstrated that an increased baseline of suPAR concentration in plasma is associated with an increased risk of tumours, cardiovascular diseases, diabetes mellitus type 2 and mortality in the general population. This association also remains after the elimination of known risk factors of the above-mentioned diseases and of death alone. C-reactive protein is also an independent predictor of cardiovascular diseases, diabetes mellitus type 2 and death. However, CRP and suPAR seem to reflect other aspects of the inflammatory status since no relationship has been found between suPAR and BMI or waist circumference. Therefore, it seems to be less associated with anthropometric parameters characteristic for the phenotype with metabolic disorders. suPAR may then be fairly useful in predicting the risk of occurrence of the above-mentioned diseases and what is the most important, it may allow obtaining early diagnosis and in consequence, enable the implementation of proper prophylactic and therapeutic procedures. It has its implications not only for the individual but also in the social and economic aspect.

suPAR and urinary tract infections

Urinary system infections, i.e. the presence of microorganisms (most often bacteria) in the urinary tract above the urinary bladder sphincter, are a frequent nephrological problem. There is no exact epidemiological data for the Polish population. The incidence of these infections is, among others, sex- and age-dependent. Urinary system infections are an significant clinical problem for the possibility of complications including acute renal failure and chronic kidney disease. In inflammations of both the lower (urinary bladder inflammation) and the upper urinary tract (pyelonephritis), increased blood concentrations of classical inflammation markers (CRP, leukocytosis) are observed [4]. And what happens with suPAR?

Florquin et al. [11] studied the urine and plasma levels of the soluble uPAR form in patients with microbiologically confirmed urosepsis, in healthy subjects after endotoxin administration (a lipopolysaccharide substance) and in a control group. The study revealed that both in the course of urosepsis and in the volunteers with experimental endotoxemia, increased suPAR concentrations were found both in urine and in plasma. Relatively higher concentrations were observed in urine. An increased expression of uPAR was also

observed on the surface of renal tubule epithelium cells in the course of pyelonephritis. The relatively higher suPAR concentrations in urine, the high proportion of urine suPAR concentration to serum suPAR concentration in the course of urosepsis and endotoxemia and the increased uPAR expression on the surface of epithelial cells of renal tubules in the course of pyelonephritis suggest that during nephritis, local production of suPAR occurs within the renal tissue. It was also found that in in vitro conditions, as a result of stimulation with interleukin-1 beta and the tumour necrosis factor-alpha (TNF-alpha), the endothelial cells of the renal tubules produce an elevated number of urokinase receptors vs. the endothelial cells not submitted to the stimulation. suPAR may, among others, inhibit urokinase binding to its specific receptor (uPAR) and in consequence, suppress the enzymatic cascade responsible for plasmin formation with its proteolytic activity. Some researchers suggest that an enhanced production of suPAR is to fight inflammation in the kidneys and protect the renal tissue against cicatrisation in the course of pyelonephritis and urosepsis. Further studies are necessary to confirm this hypothesis.

In a study by Wittenhagen et al. [22], the suPAR levels were studied in children with suspected acute pyelonephritis. The results were then compared with DMSA (technetium isotope-labelled dimercaptopurine acid)-supported renal scintigraphy. The plasma suPAR levels were significantly elevated in children with renal failure, confirmed by scintigraphy, vs. children with normal kidney functions. It suggests then that suPAR is a good marker of inflammation. According to researchers, suPAR may be useful in diagnosing acute pyelonephritis. Additionally, high plasma suPAR levels may reflect the degree of renal failure in the course of pyelonephritis. It seems then that it can be a new, valuable indicator, reflecting the degree of renal cicatrisation. Certainly, further and more extensive studies are needed to find out when a high suPAR level in blood is of a prognostic value for renal cicatrisation and chronic kidney disease.

suPAR and FSGS

Despite the great progress in medicine, glomerulonephritis is still one of the most enigmatic and unexplained groups of urinary system diseases. Numerous research projects undertaken at centres all over the world have so far, failed to determine the pathogenesis. This is also true in the case of FSGS (focal segmental glomerulosclerosis). The primary form of FSGS is a nephropathy, most often perceived as the nephrotic syndrome, which does not undergo spontaneous remission and leads to increasing glomerular impairment. It is the cause of 20–25% of nephrotic syndrome cases in white adults. Young male subjects are more often affected by the disease [4]. Primary glomerulonephritis usually leads to end-stage renal failure [23].

It is diagnosed both in physiological and in transplanted kidneys [24]. In kidney transplants, it recurs in approximately 30% of organ recipients (both adult and paediatric) [25].

Since cases of FSGS are observed in transplanted kidneys, both as de novo condition and recurrence of the disease, the concept of a humoral, circulating factor has arisen, which may induce this form of glomerulonephritis [26]. This concept is also supported by the fact of observed decreasing albuminuria as a result of treatment with plasmapheresis and by the transient nephrotic syndrome in newborns from mothers with FSGS [27,28].

Wei et al. [10] postulate a hypothesis that suPAR may be the circulating factor responsible for the occurrence of focal segmental glomerulosclerosis. Their study demonstrated that in comparison with healthy subjects, the concentrations of the soluble form of uPAR were significantly higher in patients with FSGS, having affected 2/3 of the patients with the primary form of the disease. In contrast, no significant abnormalities in suPAR levels were observed in other analysed diseases with albuminuria in their course such as the minimal change disease (MCD), membranous glomerulonephritis or the preeclamptic state. All the patients with diagnosed FSGS were divided into the following three subpopulations: primary FSGS, recurrent FSGS in a transplanted kidney and FSGS without recurrence in a transplanted kidney. It was demonstrated that the highest suPAR levels in the pretransplantation period were in those patients with FSGS in whom the disease recurred after kidney transplantation. Thus an identified suPAR concentration in serum before kidney transplantation can be an indicator of an increased risk for disease recurrence after transplantation. Serum suPAR levels were also evaluated in patients with FSGS one year after kidney transplantation. The observations clearly indicated higher levels of the soluble form of the receptor in patients with FSGS recurrence when compared to those with normal renal functions. It was also demonstrated that the levels of soluble uPAR correlated with the presence of albuminuria but not with the degree of its progression. The researchers also noted that the suPAR levels in serum remained high for one year after transplantation in patients with post-transplantation FSGS recurrence vs. the group of patients without FSGS recurrence. That study also provides some evidence that the soluble form of the receptor for urokinase (suPAR) as well as the form associated with the cell membrane (uPAR) cause some pathological activation of beta 3 integrin within podocytes. Beta 3 integrin is one of the main proteins anchoring podocytes to the basement membrane of renal glomerules. Its enhanced activation

impairs functions of the foot processes of podocytes, changes their shape and in consequence, injures the filtration membrane, leading to albuminuria and inflammation in renal glomerules. It seems to be a mechanism responsible for renal failure in the course of FSGS [29]. In healthy subjects, low activity levels of beta 3 integrin were demonstrated, while that activity was clearly enhanced both in the patients with primary and recurrent FSGS. What is more, a good correlation was shown between suPAR concentration in serum and beta 3 integrin activity in podocytes. Wei et al. [10] also studied the effect of plasmapheresis on suPAR concentration. It was demonstrated that in patients with focal segmental glomerulosclerosis, plasmapheresis could significantly decrease the suPAR levels and consequently, suppress the activity of beta 3 integrin in podocytes, eventually leading to disease remission. The authors of that study suggest a few methods of protection against podocyte lesions: 1) blocking suPAR by specific antibodies; 2) applying a beta 3 integrin inhibitor (cycloRGDfV) or antibodies against beta 3 integrin; 3) suppressing interactions between suPAR and beta 3 integrin by suPAR elimination during plasmapheresis procedures.

The identification of suPAR as a blood circulating factor causing focal segmental glomerulosclerosis throws new light on the pathomechanism of the disease and creates promising therapeutic possibilities. Nevertheless, many questions still remain unanswered. Why are no elevated suPAR levels found in approximately 30% of patients with primary and recurrent FSGS? One of the causes may be the ineffectiveness and inadequacy of currently used ELISA tests. Interactions (even with a lack of increased suPAR concentration in serum) between suPAR and the membranous form of uPAR within podocytes may be another explanation. Other causes may include the presence of podocyte gene mutations (in such cases it would be necessary to see if there is any association with suPAR or not) [30]. Finally, other still undefined factors which induce FSGS (alone or in combination with suPAR) may exist. Wei et al. [31] indicate that anti-CD40 autoantibodies (CD40 is most commonly known as a co-stimulatory molecule on antigen presenting cells) derived from patients with recurrent FSGS and full length suPAR dual treatment induce podocyte injuries and proteinuria in wild type mice. They suggest an additional role of these two circulating factors in the etiopathogenesis of podocytopathy in FSGS disease. The question is, how pathogenic human CD40 autoantibodies and suPAR interact and if they act on the same pathway such as on beta3 integrin or if there are other pathways involved. Another question which awaits an answer is which cells are the source of the soluble uPAR form in the course of FSGS (neutrophils or monocytes or B lymphocytes). Eventually, further studies are necessary to explain why patients with FSGS demonstrate an enhanced release of uPAR from the cell surface (hidden infection or long-term activation of the immune system?) [30]. New studies are unquestionably required to unveil all the unclear issues regarding the relationship between suPAR and FSGS.

suPAR and cardiovascular diseases in patients with chronic kidney disease

The whole population of patients with chronic kidney disease is characterised by a high risk of cardiovascular diseases and consequentially a high mortality rate. There is a close correlation between advanced kidney disease and the level of risk of cardiovascular complications, the risk growing with progressing renal failure [1]. Among subjects with end-stage renal failure treated with haemodialysis, cardiovascular diseases are the main cause of mortality. As has already been mentioned, out of the patients dialysed in 2009, 58% died from cardiovascular disorders [2]. The prognosis is also poor in patients with less advanced renal failure. A large study coordinated by Go [32] demonstrated that in subjects from the general population, glomerular filtration below 60 ml/min/1.73m2 was an independent risk factor of cardiovascular complications and death. In turn, a population study performed by Henry et al. [33] demonstrated that a glomerular filtration reduction by 5 ml/min/1.73m2 corresponded to a 26% risk increase of death from cardiovascular causes. The accelerated occurrence of atherosclerosis in patients with CKD results from the presence of two types of risk factors. They are both traditional (among others, age, hypertension, tobacco smoking, diabetes, hyperlipidemia) and non-traditional CKD-related (among others, anemia, disorders of calcium-phosphate metabolism and worsening vascular calcification) [34, 35]. Non-traditional factors also include coagulation disorders [36]. Thus, is there any relationship between the elevated level of the soluble form for the urokinase receptor and the incidence of cardiovascular diseases in patients with renal failure?

There is a hypothesis that both enhanced and reduced fibrinolytic activity is associated with an increased risk of cardiovascular diseases [37,38]. In turn, hemostatis disturbances are common complications of chronic kidney disease. In the course of CKD, both hypercoagulability and impaired fibrinolysis are observed, as well as increased fibrinolytic activity [39,40].

Pawlak et al. [41] demonstrated that dialysed patients with end-stage renal failure demonstrate overtly elevated suPAR levels vs. healthy subjects. What is more, the increased suPAR levels positively correlate both with uPA and the plasmin-antiplasmin (PAP) complex. PAP is a plasmin production index reflecting increased fibrinolytic activity. These positive correlations suggest a certain association between suPAR and

fibrinolytic activity in the population of haemodialysed patients.

In another study, Pawlak et al. [42] reported increased levels of suPAR and uPA in haemodialysed patients with cardiovascular (CV) disease vs. dialysed patients without a CV condition. Additionally, it was shown that both suPAR and uPA correlated with the tissue levels of thromboplastin, also called the tissue factor (TF). TF is a plasmatic coagulation factor released, among others, from endothelial cells and plays the key role in triggering coagulation cascade, which leads to fibrin formation [4]. The association between urokinase-dependent fibrinolysis and TF-dependent coagulation may contribute to an increased risk of cardiovascular diseases in patients submitted to repeated procedures of haemodialysis [42].

Pawlak et al. [43] also studied the correlation between the vascular endothelial growth factor (VEGF), and haemostasis parameters in patients with chronic kidney disease. Since VEGF participates in angiogenesis, it is of particular significance for normal blood vessel functions. On the other hand, the role of VEGF in atherosclerosis has been fairly well documented [44,45]. VEGF – by increasing TF expression – also exerts some influence on the haemostatic properties of vascular endothelial cells and modifies fibrinolysis, affecting – among others – uPAR expression [46,47]. The researchers demonstrated that an even small deterioration of renal functions was associated with an overt increase in the VEGF level and disorders of haemostasis (especially of its fibrinolytic component). These disorders are particularly enhanced in stages 4 and 5 of chronic kidney disease. In other words, increased levels of VEGF were found in the plasma from patients with CKD and a strong relationship of VEGF with renal failure indicators was also revealed [43]. An increased VEGF level was previously described in patients with atherosclerosis of peripheral and coronary arteries [44,48]. Simultaneously, increased TF levels were observed in patients with CKD, while the plasmatic levels of the TF inhibitor did not reveal any statistically significant differences. It seems that the levels of VEGF, TF and TF inhibitor in plasma may reflect the levels of these factors within atherosclerotic plaque and in consequence its activity, both prothrombotic and in term of neovascularisation [43]. They are two important mechanisms of atherosclerotic plaque growth and destabilisation [49,50]. The study also presents the relationship between VEGF and the clotting factors in the group of patients with chronic kidney disease. A strong positive correlation was demonstrated between increased VEGF levels and urokinase (uPA) and its receptor in the soluble form (suPAR). What is more, a weak positive correlation was also observed between VEGF and the plasmin-antiplasmin complex (PAP). PAP is an index of plasmin production. It is of some interest that both the accelerated PAP formation and increased VEGF levels were independently associated with the uPA/suPAR system, while not being related either to tPA or PAI-1 [43]. It is consistent with previous investigations of the researchers, demonstrating that fibrinolytic activity is mainly determined by increased levels of the plasmatic urokinase-type plasminogen activator (uPA) and the soluble form or urokinase receptor (suPAR) [51]. A significant correlation has also been found between VEGF and suPAR levels in plasma and the C-reactive protein (CRP), the classic indicator of the inflammatory state. A similar correlation has also been identified in healthy subjects, which suggests some influence of the inflammatory state on VEGF formation [43]. High suPAR levels are found, among others, in patients with urosepsis and in healthy subjects after lipopolysaccharide substance administration [11]. Thus in CKD-associated inflammatory conditions and in the presence of the angiogenesis stimulating factor suPAR levels grow, which may play some role in fibrinolysis enhancement. The results of a multifactor analysis have only confirmed that VEGF and renal function indicators (creatinine and urea) were variables independently and significantly associated with increased uPA levels. On the other hand, only VEGF was independently correlated with elevated suPAR levels. The increased formation process of the plasmin-antiplasmin (PAP) complex, reflecting fibrinolytic system activation, was also independently associated with suPAR levels. The relationship between VEGF and the uPA/suPAR system, as well as that between suPAR and PAP, suggests the abnormal angiogenesis observed in the course of CKD to be associated with hyperfibrinolysis [43]. It is recognised that the biological activity of the urokinase-type plasminogen activator depends on binding with a specific receptor – uPAR. VEGF increases the receptor expression for urokinase [47]. VEGF may also induce the activation of endothelial prourokinase, which is responsible for local VEGF-dependent fibrinolytic activation. What is more, VEGF-related fibrinolytic activity depends on urokinase and not on the tissue plasminogen activator [52]. In turn, active plasmin may stimulate the release of extracellular matrix-related VEGF [53]. Therefore, it may be assumed that in patients with CKD, the uPA/suPAR system is an important component of VEGF-induced fibrinolysis [43]. Further studies on a large group of patients are undoubtedly required to confirm the presented results.

The hypothesis of the existence of a new fibrinolysis activation mechanism in patients with chronic kidney disease is particularly interesting. This mechanism may be potentially significant for the pathogenesis of both CKD and its complications, including cardiovascular diseases. VEGF may activate the uPA/suPAR system, which leads to the production of plasmin associated with the cell surface. This is the key for

proteolysis of extracellular matrix components and for renal tissue reconstruction [52,54]. Regardless of plasmin formation, the local renal uPA/suPAR system plays an important role in the migration and adhesion of inflammatory cells to renal tissue and in the formation of oxidative free radicals, which leads to apoptosis of renal tissue cells [55]. These mechanisms may result in renal function loss and in the progression of renal failure. On the other hand, the uPA/uPAR system plays some role in the pathogenesis of vascular atherosclerosis via mediating the migration and adhesion of proinflammatory cells, in the differentiation of monocytes to macrophages, in the proliferation of vascular smooth muscle cells, in the production of oxidative free radicals or in extracellular matrix degradation [56]. These processes are associated with the progression of atherosclerosis or with atherosclerotic plaque rupture, which leads to cardiovascular episodes both in the general population and in patients with uremia [37,51]. Thus explanation and better understanding of the relationship between VEGF and the uPA/suPAR system may become very advantageous for patients with end-stage renal failure. The CV disease prevention-oriented therapy in these patients could then be tailored both to excessive fibrinolysis and abnormal angiogenesis [43].

Between 30–50% of patients with end-stage renal disease (ESRD) have an activated inflammatory response [57]. Chronic inflammation is another non-traditional risk factor of atherosclerosis in dialysis patients. In this group of patients, compared to the controls, an increased level of suPAR is observed [41,58]. The causes of inflammation are multifactorial and they include patient-related factors (among others an underlying disease, comorbidity, infections, obesity) and haemodialysis-related factors which mainly depend on membrane biocompatibility and dialysate quality [59]. Inflammation alone or in combination with a low protein intake plays a significant role in causing hypoalbuminemia and malnutrition in CKD patients. High levels of pro-inflammatory cytokines may cause muscle wasting by stimulating protein catabolism via the ubiquitin-proteasome pathway, by reducing albumin synthesis or by inhibiting appetite. Inflammatory markers, such as CRP and interleukin-6 (IL-6), are strong predictors of malnutrition in patients on dialysis. Malnutrition may worsen a patient's outcome by aggravating existing inflammation and heart failure and accelerating atherosclerosis. Various studies show signs of malnutrition in 23–76% haemodialysis patients. Available evidence suggests that inflammation can be associated with endothelial dysfunction, which may accelerate atherosclerosis. In malnourished and inflamed patients increased oxidative stress occurs. Strong relations between malnutrition, inflammation and atherosclerosis in ESRD patients suggest the presence of a syndrome called malnutrition, inflammation, and atherosclerosis (MIA). A central role in this vicious circle is played by pro-inflammatory cytokines, among others interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-alpha). Cytokines are generated in response to factors such as chronic heart failure and/or fluid overload, as well as infectious/inflammatory co-morbid diseases [60,61].

Almroth et al. [58] demonstrated that all haemodialysis patients had significantly elevated levels of suPAR as compared to the controls, even after age and gender correction. Furthermore, in the patient group a significant correlation was found between sclerostin and suPAR [62]. Sclerostin is an antianabolic bone factor released by osteocytes. This marker increases with declining renal function and is elevated in haemodialysis patients [63,64]. It may be also associated with vasculitis and vascular calcification [65]. A significant correlation also was identified between suPAR and two pro-inflammatory cytokines TNF-alpha and interleukin-18 (IL-18) [62]. It is assumed that the pro-inflammatory cytokines play an important pathogenic role in congestive heart failure (CHF). The majority of dialysis patients experience cardiomyopathy. Left ventricular hypertrophy and systolic dysfunction lead to CHF and a reduced life expectancy. The failing heart produces large quantities of TNF-alpha. A direct relationship has been shown between the level of TNF-alpha expression and the severity of CHF. Tumor necrosis factor-alpha administered to animal models at concentrations observed in congestive heart failure produced effects parallel to those seen in patients with CKD. Notably, the development of congestive heart failure was averted by anticytokine therapy. Volume status normalization is associated with significantly decreased edotoxin levels, which supports the possible association between CHF and inflammation [60]. Interleukin-18 may be involved in vascular calcification. High IL-18 levels might result in atherosclerotic plaque progression and increased vulnerability of coronary or other arteries [66]. Sclerostin, TNF-alpha and IL-18 correlated both with suPAR and with each other. The interplay within reactive factors could be possibly related to the progression of vessel disease and long-term prognosis in haemodialysis patients. Further studies are necessary to evaluate the role of these immunological markers, especially suPAR, in patients with atherosclerosis treated with haemodialysis [62]. A better understanding of the pathogenetic processes involved will help to reduce the unacceptably high morbidity and mortality rate in patients with ESRD. It is worth noting that the onset of atherosclerosis certainly takes place much earlier than the onset of renal replacement therapy. The majority of patients starting dialysis already have signs of advanced atherosclerosis. Therefore the time to prevent CVD is the predialysis phase [60].

SUMMARY

Taking into account its properties, suPAR seems to be a good marker, fairly useful in everyday clinical practice. In the population of healthy subjects, it is identified by low titres both in plasma and in urine [11]. Unlike other markers (e.g. CRP), its levels either do not undergo circadian variations at all or they are minimal (assayed each 20 minutes for 24 hours) [67]. Its concentration is stable, even in the case of repeated freezing and thawing of serum samples [68]. Its blood levels remain elevated for a longer time period after hospital admission, revealing a falling tendency only after a few weeks [20]. Therefore, its measured results are independent of when blood samples are collected. It has been demonstrated that its serum concentrations positively correlate with the concentrations of other markers of the inflammatory state (TNF-alpha, CRP and procalcitonin) and with disease severity evaluating scales (APACHE II, SOFA, SAPS2). There is also a positive correlation between suPAR concentrations and organ injuries. Furthermore, in the case of renal lesions the correlations are with creatinine, urea and cystatin C and in the case of hepatic changes suPAR concentrations correlate with bilirubin, GGTP, base phosphatase and albumin [20]. When blood sampling is for any reason difficult, one may assay the suPAR concentration in urine as a strong, positive correlation has been identified between plasma and urine concentrations both in healthy subjects and affected patients [69,70]. It is also important from the practical point of view that simple ELISA-based tests may be used to assay suPAR concentrations both in blood and urine.

The soluble form of the urokinase-type plasminogen activator receptor is a good, although non-specific inflammation marker. Its levels in physiological fluids are elevated in various medical conditions [14,16, 18,19]. Interesting, the latest studies show that elevated plasma suPAR levels were associated with incident chronic kidney disease (defined as an estimated glomerular filtration rate (eGFR) < 60 ml per minute per 1.73 m^2) and a more rapid decline in eGFR in persons with normal kidney function at the baseline [71]. Thus, in the light of the above-mentioned studies, can common suPAR assays be recommended? It is not yet possible but other studies are underway which may help explain the presently unclear issues concerning the relationship of suPAR with urinary tract infections, FSGS, or the role of suPAR in cardiovascular diseases of patients with chronic kidney disease. The results of these studies may introduce suPAR assay into the diagnostic apparatus of selected kidney diseases, making it a routine diagnostic tool.

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