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Novel early markers of chronic kidney disease

Nowe, wczesne markery przewlekłej choroby nerek

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Abstract

Chronic kidney disease is an irreversible kidney damage caused by structural or functional renal impairment and persisting for more than 3 months. It is usually accompanied by albuminuria, proteinuria, abnormal histopathological and imaging findings as well as a drop in glomerular filtration rate below 60 mL/min/1.73 m^2. Due to the increasing number of patients, chronic kidney disease is referred to as "the epidemic of the 21st century." Early diagnosis allows for effective therapeutic intervention, which makes it possible to inhibit pathological processes and prevent disease in the future. Diagnostic difficulties in detecting early stages of chronic kidney disease are due to their asymptomatic nature and the fact that the markers widely used for renal function assessment are not very sensitive. Therefore, new, early, sensitive and specific markers of renal damage, whose introduction in everyday clinical practice would give a chance of a diagnosis at the very onset of the disease, before irreversible changes occur, are currently being sought. Although the results of scientific research are ambiguous, some of the candidate protein markers seem very promising. These include uromodulin, KIM-1, NGAL-1, NAG, FGF23, RBP4 and suPAR. The aim of the paper was to present a review of the latest research on the use of novel protein markers in the diagnosis of chronic kidney disease in paediatric and internal medicine patients.

Keywords: chronic kidney disease, uromodulin, KIM-1, FGF23, NGAL, NAG

Streszczenie

Przewlekła choroba nerek to stan nieodwracalnego uszkodzenia nerek wynikający z zaburzeń w ich budowie lub funkcji, utrzymujący się powyżej 3 miesięcy. Zwykle towarzyszą mu: albuminuria, proteinuria, odchylenia w badaniach histopatologicznych i obrazowych oraz spadek filtracji kłębuszkowej poniżej 60 ml/min/1,73 m^2. Przewlekła choroba nerek ze względu na stale rosnącą liczbę pacjentów z tym rozpoznaniem nazywana jest epidemią XXI wieku. Ustalenie rozpoznania na wczesnym etapie choroby daje możliwość wdrożenia skutecznej interwencji terapeutycznej, dzięki czemu można zahamować procesy patologiczne oraz nie dopuścić do rozwoju choroby w przyszłości. Trudności diagnostyczne w wykrywaniu wczesnych stadiów przewlekłej choroby nerek wynikają z ich bezobjawowego przebiegu oraz z faktu, że markery powszechnie stosowane do oceny funkcji nerek nie charakteryzują się zbyt dużą czułością. Dlatego właśnie trwają poszukiwania nowych, wczesnych, czułych i specyficznych markerów uszkodzenia nerek, których wprowadzenie do codziennej praktyki klinicznej dawałoby szansę uchwycenia początku choroby, zanim doprowadzi ona do nieodwracalnych zmian. Wyniki badań naukowych jak na razie nie są jednoznaczne, jednak część proponowanych do zastosowania markerów białkowych wydaje się bardzo obiecująca. Należą do nich: uromodulina, KIM-1, NGAL-1, NAG, FGF23, RBP4 oraz suPAR. Celem niniejszej pracy jest przedstawienie przeglądu najnowszych badań dotyczących zastosowania nowych markerów białkowych w diagnostyce przewlekłej choroby nerek w grupach pacjentów pediatrycznych i internistycznych.

Słowa kluczowe: przewlekła choroba nerek, uromodulina, KIM-1, FGF23, NGAL, NAG

INTRODUCTION

Chronic kidney disease (CKD) is an irreversible kidney damage caused by structural or functional renal impairment and persisting for more than 3 months. It is usually accompanied by albuminuria, proteinuria, abnormal histopathological and imaging findings as well as a drop in glomerular filtration rate below 60 mL/min/1.73 m^2[1]. Due to the constantly growing number of patients with CKD, the disease is referred to as "the epidemic of the 21st century." It is estimated that 600 million people are affected worldwide, including about 4.3 million in Poland[1]. The incidence of CKD in children under 16 years of age is 1.5–3 per 1,000,000[2]. Diagnostic difficulties at early stages of CKD are, among other things, due to their asymptomatic nature[2]. However, only early diagnosis of CKD allows for the implementation of effective therapeutic intervention to delay or inhibit disease progression[3]. Currently used diagnostic markers for CKD, i.e. creatinine and urea levels, GFR, albuminuria and proteinuria, do not show high sensitivity[3].

GFR reflects the number of functional nephrons. Although GFR measured by inulin clearance is the gold standard[4], the method is not used in clinical practice due to its complex nature, i.e. a continuous intravenous infusion of exogenous inulin and bladder catheterisation. GFR may be also calculated based on the clearance of exogenous creatinine, a chemical compound formed as a result of enzymatic degradation of creatinine synthesised in the muscles[5]. This requires a 24-hour urine collection which often yields inaccurate results due to missed sampling or episodes of incontinence[6]. Furthermore, tubular excretion of endogenous creatinine may cause falsely increased GFR[6]. The limitations in estimating GFR using a 24-hour urine collection were the basis for the development of a formula for GFR estimation based on serum creatinine levels[6]. The Schwartz formula, which was developed in the 1980s of the 20th century, uses serum creatinine [mg/dL] measured by the Jaffe assay, height [cm] and the *k*-coefficient, which is proportional to muscle mass and age- and sex-dependent[6]:

$$\text{GFR [mL/min/1.73 m}^2\text{]} = k \times \text{height [cm]} / \text{serum creatinine [mg/dL]}$$

However, it was found that the error of GFR calculated from serum creatinine is about ±20% and ±30–40% in children[5]. Furthermore, GFR may be measured in children at least 2 years of age due to urinary tract immaturity, and thus underestimated GFR[1]. The measurement of endogenous creatinine also has its limitations. Creatinine levels depend, among other things, on muscle mass[5] and diet[7].

Albuminuria and proteinuria, which are important parameters for assessing the stage of CKD in adults, are not always applicable in paediatric practice. In accordance with the 2012 KDIGO guideline[1] and based on National Health and Nutrition Examination Survey III (NHANES III) findings[8], the range of values for albuminuria in children is the same as in adults. However, these criteria are of no use in children <2 years due to urinary tract immaturity and lower protein absorption in the proximal tubule compared to adults[1]. It was shown, on the other hand, that proteinuria correlates with decreased GFR better than albuminuria[9,10]. Furthermore, CKD in children is often due to congenital renal anomalies associated with tubular loss of albumins; therefore, albuminuria is a less sensitive marker of renal function[10].

Due to the above mentioned limitations of the widely used renal function markers, there is an ongoing search for new, early, sensitive and specific markers of renal damage, whose introduction in everyday clinical practice would give a chance to capture the onset of the disease before it leads to irreversible changes. Although the results of scientific research are ambiguous, some of the candidate proteins seem very promising for the diagnosis of CKD. These markers include uromodulin, KIM-1, FGF23, NAG, NGAL-1, suPAR and RBP4.

UROMODULIN

Uromodulin (Umod), or the Tamm–Horsfall protein, is a 95 kDa glycoprotein synthesised by the epithelial cells of the distal tubules and the ascending limb of the loop of Henle[11]. Since slight amounts of uromodulin are also released into the interstitial tissue, the marker is found in the blood. Under physiological conditions, it is the most abundant urinary protein, whose release rate is estimated at 75 mg/24 h[12]. The protein has many functions, e.g. it covers the epithelium of the nephron tubules and, as a defensin, it protects the urinary tract against infections as well as prevents stone formation in the urinary tract[12,13]. Furthermore, due to its effects on the $Na^+/K^+/Cl^-$ ion channels, the protein is likely to contribute to water and electrolyte homeostasis in the loop of Henle[14]. Recently, uromodulin has also been found to be a useful marker of renal damage. A reduced number of nephrons due to, among other things, renal tubule atrophy or CKD-related fibrosis, correlates with reduced urine and serum uromodulin levels[15]. In their prospective study in 426 adult patients, Steubl et al. demonstrated the usefulness of serum uromodulin (sUmod) for monitoring renal function in CKD patients[16]. A gradual drop in sUmod correlated with the deterioration of renal function, which was estimated at a mean of 111.0 ng/mL in stage 1 CKD patients, 107.3 ng/mL in stage 2 CKD patients, 71.0 ng/mL in stage 3 CKD patients, 38.1 ng/mL in stage 4 CKD patients, and 24.8 ng/mL in stage 5 CKD patients, was observed. In another study, Scherberich et al. showed a correlation between decreased sUmod, cystatin C and creatinine urine levels and GFR[12]. Also, similar sUmod levels were observed between adults and children with stage 0 CKD. No sex-related differences were found[12].

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Tan et al. also demonstrated a relationship between sUmod and GFR as well as showed that patients with low sUmod levels are at a higher risk of end stage renal disease (ESRD) in the future[17].

KIM-1

Kidney injury molecule-1 (T-cell immunoglobulin, mucin-containing molecule) is a 104 kDa type 1 transmembrane protein found in the apical membrane of proximal tubule cells[18,19]. Since the KIM-1 ectodomain (91 kDa) is cleaved from the protein molecule by metalloproteinases in response hypoxia, ischaemia or toxic damage to the renal tubules, its presence in the serum and urine is a marker of acute renal failure[19,20]. Ichimura et al. showed the usefulness of KIM-1 as an early marker for nephrotoxicity. Increased KIM-1 urinary levels were observed in patients on cisplatin much earlier than increased serum creatinine[21]. Furthermore, the presence of KIM-1 in the urine indicates proximal tubule damage as the protein is involved in phagocytosis[22]. KIM-1 is therefore involved in structural and functional regeneration of the nephron tubule epithelium[23]. Based on this finding, KIM-1 was also found useful as a marker for CKD. In their international prospective CRISIS study, Alderson et al. showed in a group of 1,982 adult patients with stage 3–5 CKD that the presence of KIM-1 in the serum increases the risk of progression to ESRD[24]. In their analysis of 5 cohort studies in USA and Sweden, Waikar et al. found a strong correlation between albuminuria and elevated serum KIM-1[25]. De Silva et al. showed the usefulness of KIM-1 for the detection of early CKD of unknown aetiology in Sri Lanka's population[26]. Furthermore, this protein may be used in both, the diagnosis and progression assessment of diabetic nephropathy in patients with type 1 diabetes[25].

NGAL-1

Neutrophil gelatinase-associated lipocalin 1 (siderocalin) is a 25 kDa protein synthesised and released mainly by leukocytes, epithelial cells of the Henle loop and collecting tubules[18,19]. However, it is also released by prostate, tracheal, lung, stomach, colon, uterus and bone marrow cells[19]. NGAL-1 belongs to acute phase proteins. In the human body, it exerts bacteriostatic effects by binding bacterial siderophores, and thus inhibiting bacterial iron acquisition. The effects of NGAL-1 on siderophore–iron complexes are also associated with the processes of cellular differentiation and proliferation[19]. The protein plays an important role in embryogenesis by transforming nephron mesenchymal cells into epithelial cells[18]. Its increased release by renal epithelial cells is observed in response to their damage[24]. The presence of NGAL-1 in the serum and urine is a recognised marker of acute renal failure[27,28]. NGAL-1 also mediates mitotic divisions of epithelial cells dependent on the epidermal growth factor receptor (EFGR), which induces nephron cell proliferation, gradual loss of function and progression of CKD in response to hypoxia[29]. Bolignano et al. assessed the usefulness of NGAL-1 as a novel, independent marker of CKD progression. Its serum levels were increased already at baseline in the study group (patients with stage 2–4 CKD) compared to controls (CKD-free patients). In this study, serum and urine NGAL-1 levels were inversely correlated with GFR[30]. In the CRISIS study, Alderson et al. also found NGAL-1 to be a marker of CKD progression; however, they found it to be less precise in the assessment of progression compared to conventional markers[24]. Since NGAL-1 measurements were more reliable in patients with stage 3 CKD than in patients with stage 4 or 5 CKD, NGAL-1 was considered to be a useful marker for the diagnosis of early CKD[25]. In their small study in the paediatric population, Mitsnefes et al. showed a correlation between NGAL-1 and Schwartz GFR, confirming the usefulness of NGAL-1 for the assessment of renal function in paediatric CKD patients[31].

NAG

N-acetyl-β-D-glucosaminidase is a lysosomal enzyme released by the microvilli of the proximal tubular epithelial cells. NAG is a 130–140 kDa protein, which makes its filtration through the glomeruli impossible[32].

Increased release of NAG in the urine is due to tubular cell injury and represents a useful marker for the diagnosis of renal damage and nephrotoxicity[34]. Jungbauer et al. demonstrated in their study in 149 adult patients with heart failure that NAG was a useful independent marker of CKD progression[35]. It was also shown that NAG and KIM-1 are better correlated with the risk of progression to ESRD when assessed together rather than independently[35]. Increased urinary levels of NAG are also observed in other nephrological pathologies, such as idiopathic nephrotic syndrome[36], vesicoureteral reflux and hydronephrosis[37] as well as urinary tract infection[38]. Diabetes Control and Complications Trial (DCCT) additionally showed that NAG is well correlated with albuminuria in patients with type 1 diabetes and may be useful for assessing the risk of diabetic nephropathy in this group of patients[39].

FGF23

Fibroblast growth factor 23 is a hormone produced by osteoblasts and responsible for regulating mineral and bone metabolism[40]. It inhibits the release of parathyroid hormone (PTH) by forming a complex with FGF receptor and the Klotho protein. It reduces serum phosphates by affecting sodium phosphate co-transporter in the proximal tubules, and decreases active vitamin D (1,25-dihydroxycholecalciferol) levels by inhibiting 1-α-hydroxylase[40]. Therefore, high serum levels of calcium and phosphate, PHT and 1,25-dihydroxycholecalciferol are factors regulating the release

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of FGF23. However, elevated FGF23 levels are also observed in oxidative stress, inflammation, overactivation of the renin–angiotensin–aldosterone system (RAAS) and iron deficiency[41,42]. High levels of FGF23 in CKD correlate with renal adaptation to the reduced phosphate excretion in the urine[43]. The CRIC study, which was conducted by Isakova et al. in 3,879 patients with stage 2–4 CKD, showed that elevated FGF23 levels were correlated with a high risk of progression to ESRD[43]. FGF23 is also likely to be a marker of an increased risk of mortality among patients with CKD[43]. Tranæus Lindblad et al. assessed serum FGF23 levels in 74 paediatric patients with CKD. They confirmed the relationship between elevated FGF23 and reduced GFR, and thus CKD progression in paediatric patients despite good control of serum phosphate[44]. In their independent studies, Lukaszyk et al. and Pavik et al. demonstrated the usefulness of FGF23 as a marker of early CKD[45,46]. Other studies also showed the usefulness of this hormone for cardiovascular risk assessment in patients with CKD – FGF23 levels correlated with left ventricular hypertrophy, as confirmed by echocardiography. Various sources indicate that FGF23 may also play a role in the diagnosis of preclinical atherosclerosis in patients with CKD[47].

RBP4

Retinol binding protein 4 (RBP4) is an adipokine produced in the liver and the adipose tissue. It plays an important role in modulating insulin signalling pathway, and is therefore involved in insulin resistance in obese and type 2 diabetic patients[48]. RBP4 is also responsible for transporting retinol (ROH, vitamin A) from hepatic reservoirs to target cells and tissues[49]. Due to its small molecular weight of 21 kDa, the RBP4–ROH complex forms a complex with transthyretin (TTR), a 55 kDa protein, and thereby avoids glomerular filtration[50]. The RBP4–TTR complex breaks down upon delivery of retinol into the target tissue, and the RBP4 undergoes glomerular filtration followed by degradation in the proximal tubule[49,50]. Several independent studies showed the usefulness of RBP4 measurement in the diagnosis of CKD. In their study in 51 patients with CKD and 30 healthy individuals, Xun et al. found statistically significantly higher serum RBP4 levels in the CKD group. Furthermore, RBP4 levels were well correlated with serum urea and creatinine levels[51]. In their study in 54 patients with stage 2–5 CKD and 45 healthy individuals, Henze et al. showed the presence of RBP4-LL in CKD patients and significantly elevated RBP4-LL during progression to subsequent stages of the disease[50]. Recently, the importance of urinary fractional excretion of RBP4 (uRBP4) in the diagnosis of CKD has been emphasised[52]. Musiał et al., who assessed a group of 70 children with stage 1–5 CKD, found increased urinary excretion of RBP4 in CKD patients, which correlated with the stage of the disease, most likely due to the damage of nephron tubules and their inability to perform compensatory reabsorption of RBP4[52].

suPAR

Soluble urokinase plasminogen activator receptor (suPAR) originates from the cleavage of the membrane-bound uPAR (CD87) protein, which is expressed, among other things, on immune and endothelial cells as well as podocytes[53,54]. Both the circulating and the membrane-bound form play a role in mediating immune processes by activating chemotaxis and proteolysis. Furthermore, they are involved in intercellular adhesion and the movement of immune cells[54]. The circulating form, i.e. suPAR, is easily detectable in plasma, serum, urine and other bodily fluids[55]. Increased suPAR levels are found in acute and chronic inflammation[54,56,57], coronary artery disease[58], and type 1 diabetes[59]. It has also been recently found that suPAR levels are elevated in focal segmental glomerulosclerosis and diabetic nephropathy[55]. In their prospective study in a group of 3,683 patients, Hayek et al. showed the usefulness of suPAR as a marker of CKD progression. Additionally, the authors found that elevated suPAR in individuals with normal GFR were associated with a significantly higher risk of CKD in the future[55]. Other large studies in paediatric patients, i.e. ESCAPE (1999–2007) and 4C (2010–2016), also demonstrated the usefulness of serum suPAR measurement for assessing the risk of CKD progression in children[60].

CONCLUSIONS

In this review paper, we presented novel, early diagnostic markers for CKD by collecting data from the latest research in paediatric and internal medicine patients.

Since none of these markers seems universal, sensitive and specific enough, attempts are made to create panels of markers. Mwasongwe et al., who assessed the diagnostic utility of a panel of markers (adiponectin, aldosterone, B-type natriuretic peptide, cortisol, high sensitivity C-reactive protein, endothelin, homocysteine, and rennin in the serum) for detecting CKD in a group of 2,813 adult patients, confirmed its role in monitoring CKD and its slight superiority over standard methods for diagnosing early stages of CKD[61]. Mihai et al., who assessed two panels of markers: inflammatory mediators [interleukin 6 (IL-6), tumour necrosis factor α, (TNF-α)] and mineral and bone disorder biomarkers (OPG, OPN, OCN, FGF23 and fetuin-A), showed that these markers are more clinically useful in the diagnosis of early CKD when used as panels rather than independently[3].

Since there is still much to be discovered in the context of novel, early CKD markers, further prospective studies are needed so that the markers can be used in everyday clinical practice in the future.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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