Review

Proximal tubule dysfunction in renal diseases - diagnostic significance of proteomics and biomarkers

Disfuncția tubulară proximală în boala renală - importanța diagnostică a proteomicii şi biomarkerilor

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Abstract

At present time, clinical practice requires advanced studies of plasma and urinary proteomics which should allow the identification, selection, and implementation of plasma and urinary biomarkers useful in the diagnosis of acute and chronic renal diseases, as well as of drug-induced nephrotoxicity. The importance of these biomarkers also resides in their prognostic value and the posibility of their repeated and dinamic assessment, in order to detect early the progression of an acute renal disease to chronic kidney disease, and of the later one to its final stages.In the present paper urinary biomarkers and proteomics, and their application in the accurate diagnosis of tubular lesions in various settings, (such as early diabetic nephropathy, acute kidney injury, glomerular nephropathies, polycystic kidney disease, renal transplantation, Balkan endemic nephropathy, and preeclampsia), are discussed in view of the clinical expertise of the authors in this field.

Keywords*: biomarkers, proteomics, tubular lesions*

Rezumat

În prezent, practica clinică necesită studii complexe de proteomică plasmatică şi urinară, care să permită identificarea, selectarea şi implementarea de biomarkeri plasmatici şi urinari, utili în diagnosticul bolilor renale acute şi cronice, precum şi a nefrotoxicității medicamentoase. Importanța acestor biomarkeri rezidă şi în valoarea lor prognostică, dar şi în posibilitatea unor determinări repetitive, în dinamică, cu scopul de a detecta precoce progresia unei boli renale acute spre cronicizare şi a unei boli renale cronice spre stadiile finale. În articolul de față se prezintă biomarkerii şi elementele de proteomică urinară cu aplicare în cadrul unui diagnostic de acurateţe al leziunilor tubulare în variate condiții clinice, precum nefropatia diabetică incipientă, leziunea re-

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nală acută, nefropatiile glomerulare, rinichiul polichistic, transplantul renal, nefropatia endemic balcanică şi preeclampsia). Aceste aspecte sunt discutate în raport cu experienţa în domeniu a autorilor.

Cuvinte cheie: *biomarkeri, proteomică, leziune tubulară*

Urinary proteomics in renal diseases

The term *proteom* implies the total of proteins present in different biological compartments. These compartments may be represented by the whole organism, by a certain tissue, cell or cellular organelle, as well as by biological fluids, such as urine (1). *Proteomics*, is a technology which tries to define the proteic structures contained in these compartments, aims mainly at identifying biomarkers which may be useful in the diagnosis, prognosis and monitoring of different diseases, including renal diseases.

Proteomic studies may be classified as comparative studies (which try to establish the calitative and quantitative differences between the proteins of the explored compartments), and as descriptive studies (which aim at identifying proteins separated in distinct fractions) (1-3).

Urinary proteins result from plasma filtration, vascular lesions, alterations of the tubular metabolism, and from reabsorption and/or secretion of proteins by cells of the urinary tract. The analysis of proteins is performed either from the urine, or from the urinary exosomes (intracellular vesicles released by the renal epithelial cells as a consequence of intracellular multivesicular bodies fusion with the apical plasma membrane (1).

Urinary proteomics may be used for the accurate diagnosis of tubular lesions in various settings, such as *early diabetic nephropathy, acute kidney injury, glomerular nephropathies, polycystic kidney disease, renal transplantation, Balkan endemic nephropathy, and preeclampsia* (entities which will be discussed in detail in part 2 of the article).

A proteomic analysis of urinary proteins performed in type 2 diabetes mellitus patients with normo-, micro-, and macroalbuminuria showed that several types of urinary proteins were up-regulated, while others were down-regulated.

Variations in the upregulation and downregulation of these proteins were highly predictive of diabetic chronic kidney disease (CKD) progression (4).

The utility of urinary biomarkers identification in the course of both type 1 and type 2 diabetes mellitus derives from the variability in time of albuminuria, from normo- to micro- and macroalbuminuria and reversely, from micro- to normoalbuminuria. Also, highly significant is the stage of albuminuria (5) or even of normoalbuminuria (6-9).

In this context, there can be be defined urinary biomarkers of prediction, urinary biomarkers of detection of spontaneous regression from micro- to normoalbuminuria, biomarkers of regression under specific therapy, and biomarkers of progression of diabetic nephropathy and renal function decline (10).

In patients with *acute kidney injury (AKI)*, proteomic studies of urinary proteins have revealed various proteins and peptide fragments whose presence in the urine of these patients may define the real onset of the renal lesion. Also, urinary proteomics allows the differentiation of early AKI from established AKI (11).

Urinary proteomics deserves special attention in the diagnosis of *preeclampsia.* A multitude of differential proteins have provided a clue for investigating the mechanism of proteinuria development in preeclampsia. Low urinary angiotensinogen levels were useful for identifying preeclampsia (12,13). Among the biomarkers studied, fibrinogen alpha chain, collagen alpha chain, and uromodulin fragments are of some interest. The markers appear to predict preeclampsia at gestational week 28 with good confidence but not reliably at earlier time points (weeks 12-16 and 20). After prospective validation in other cohorts, these markers may contribute to better prediction, monitoring, and accurate diagnosis of preeclampsia (14).

Urinary biomarkers in the diagnosis of proximal tubule dysfunction

Biological markers, known under the terminology of biomarkers, allow the identification of normal and abnormal processes which occur in various clinical settings, including renal diseases. Biomarkers can be used for the predisposition evaluation towards a certain disease, for detection of biological abnormalities, early diagnosis of renal diseases, assessment of prognosis and progression of a disease, and in assessing the response to treatment protocols.

It should be underlined that biomarkers are not involved in the pathogenesis of diseases, being used only as diagnostic and prognostic markers. Recent proteomic studies have identified new urinary biomarkers that include intact or fragmented proteins, which selectively increase or decrease in the course of renal diseases; patterns of proteins which represent specific indicators for various renal diseases; patterns of proteins which have a predictive value for the progression of acute and chronic renal diseases (15,16).

Chronic kidney disease

Diabetic nephropathy

The assessment of proximal tubule dysfunction in the course of diabetes mellitus comprises a panel of urinary biomarkers which allow establishing the early diagnosis of diabetic CKD, even in the stage of normoalbuminuria. The increase in the level of these biomarkers has a predictive value for the occurrence of early diabetic nephropathy.

According to the tubular theory regarding the mechanism of albuminuria in the course of diabetes mellitus and the fact that proximal tubule dysfunction is present in normoalbuminuric patients and precedes the occurrence of albuminuria, urinary biomarkers of proximal tubule dysfunction yield a substantial benefit in the diagnosis and progress of diabetic nephropathy. A vast number of experimental and clinical studies associate the biomarkers of proximal tubule dysfunction with normoalbuminuria, as well as with their utility in the follow-up of albuminuria variability from normo- to microalbuminuria, as well as the possibility to revert micro- into normoalbuminuria (5,17).

Urinary alpha1-microglobulin is a marker of early proximal tubule dysfunction utilized in various renal diseases, including diabetic nephropathy. This is a protein with low- molecular weight detected in blood and urine as an unbound form, and as a bound form with IgA and albumin. Alpha$_1$-microglobulin is filtered freely by the glomeruli and reabsorbed by the proximal tubule (5). Increases in the levels of urinary alpha$_1$-microglobulin has been signaled in normoalbuminuric patients with type 1 diabetes mellitus (18,19) and type 2 diabetes mellitus (8,20,21).

It should be underlined that the increase in urinary alpha$_1$-microglobulin preceeds the occurrence of normoalbuminuria in both type 1 and type 2 diabetes mellitus, a fact which supports the defining intervention of the proximal tubule in glomerular filtered albumin processing. Thus, although renal lesions may be present at the glomerular level before the tubulointerstitial lesions, microalbuminuria does not become detectable as long as the proximal tubule maintains its structural and functional integrity. It is well established by now that the role of the proximal tubule in glomerular filtered albumin processing is fundamental, in the frames of the retrieval and degradation pathways of albumin at the level of the proximal tubule (8,19-21).

Urinary beta$_2$-microglobulin is a low-molecular weight protein filtered freely at glomerular level and reabsorbed almost entirely by the proximal tubule. This is utilized as an indicator of proximal tubule dysfunction in various renal diseases, including diabetic nephropathy (5). Increases in the levels of urinary beta$_2$-microglobulin may occur in normoalbuminuric patients with type 2 diabetes mellitus (21-23), thus proving that proximal tubule dysfunction is dissociated from glomerular endothelial dysfunction (8).

In the clinical practice, the correlations between urinary alpha$_1$-microglobulin and urinary beta$_2$-microglobulin are indicative of proximal tubule dysfunction in early diabetic nephropathy, before the stage of microalbuminuria (8,21,24).

N-acethyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme of 140 kDa molecular weight localized in the brush border of the proximal tubule cell, and released in the urine as a consequence of proximal tubule lesions (5,25). The levels of NAG also increase in proximal tubule dysfunction evidenced in normoalbuminuric patients with type 1 diabetes mellitus (19,26). In a recent study performed in patients with type 1 diabetes mellitus it has been demonstrated that the transition from micro- to normoalbuminuria is associated with decreased urinary elimination of NAG. This fact supports the hypothesis according to which the earliest renal lesion in type 1 diabetes mellitus is at tubular level and not at glomerular level (27).

Neutrophile gelatinase-associated lipocalin (NGAL) is a lysosomal enzyme localized in the proximal tubule, of 25 kDa molecular weight, and resistant to the activity of proteases. NGAL levels in the urine and plasma increase in the course of acute kidney injury, renal lesions induced by ischaemia/reperfusion, nephrotoxicity, and CKD. Recently, NGAL proved reliable in the diagnosis of early diabetic nephropathy (18). Urinary NGAL levels correlate with proximal tubule dysfunction and renal function in type 2 diabetes mellitus, and have a predictive value for the transition from normo- to microalbuminuria and the occurrence of early diabetic nephropathy (28). Urinary NGAL may be a promising marker for monitoring renal impairment in short-term type 2 diabetes mellitus, thus showing that tubular damage is common in this category of patients (29).

Kidney injury molecule-1 (KIM-1) is a membrane type 1 glycoprotein which contains, in its extracellular domain, immunoglobulin- and mucin-like dimers, with N- and O-glycosilated sites. KIM-1 is expressed at the apical pole of the membrane of the proximal tubular cells, while its ectodomain is clived and released in the tubular lumen for urinary excretion. KIM-1 is not detected in the normal urine, but it is expressed in large amounts in proximal tubule lesions related to various renal diseases as to the effects of several toxins (5,25).

Increased levels of KIM-1 have also been demonstrated in patients with type 1 diabetes mellitus, in whom the transition from microalbuminuria to normoalbuminuria was accompanied by the decrease in urinary KIM-1 expression. This observation constitutes an argument which favors proximal tubule dysfunction as a preceding event, before glomerular lesions in the course of type 1 diabetes mellitus (27).

Higher urinary tubular damage markers, such as NGAL and KIM-1, were found in type 2 diabetes mellitus patients with glomerular hyperfiltration, probably a direct proof that glomerular hyperfiltration is a deleterious factor for diabetic nephropathy (29).

Liver-type fatty acid-binding protein (L-FABP) is a urinary marker of proximal tubule lesion, its increased levels being detected in all patients with type 1 diabets mellitus, even in patients without elements of glomerular lesions or albuminuria. Variations in the levels of L-FABP have a predictive value for the progression from normo- to microalbuminuric in patients with type 1 diabetes mellitus (30). Other urinary biomarkers utilized in the diagnosis of proximal tubule dysfunction in type 2 diabetes mellitus are ***fractional excretion of magnesium*** (31), and ***α-glutathion-S-transferase*** (32).

More recently, it has been forwarded the hypothesis according to which ***albuminuria*** per se may be considered as a nephrotoxin and a proximal tubule lesion biomarker. These data are maintained by studies which try to define potential toxins with direct action upon the proximal tubule (Predictive Safety Testing Consortium, US Food and Drug Administration, European Medicines Agency) (33).

Starting from the observation that normal glomeruli filter high amounts of albumin which is

reabsorbed and processed by the proximal tubule, albuminuria occurs when there is an underlying proximal tubule dysfunction (34,35), which may also be induced by albuminuria or peptide fragments derived from the glomerular filtered albumin. The peptides which derive form advanced glycation end-products (AGE_S), such as glycated albumin, might have a potential nephrotoxic effect on the proximal tubule, thus contributing to the occurrence of proximal tubule dysfunction in the course of diabetes mellitus (26). The same nephrotoxic potential may display yet incompletely identified peptides (5).

Glomerular nephropathies

Urinary biomarkers have proved their utility in monitoring primary and secondary chronic glomerulonephritides. Tubulointerstitial lesions are significant in the course of chronic glomerular nephropathies and are related to the degree of renal function decline. Tubular dysfunction may be evidenced by increased eliminations of *leucin-aminopeptidase* and *lactic dehydrogenase* in patients with acute oligoanuric glomerulonephritis. These tubular enzymes have revealed the important contribution of tubular lesions in the occurrence of acute renal failure in the course of acute oligoanuric glomerulonephritis (36).

Some toxic effects of proteinuria on tubular epithelial cells have been considered to be responsible for the tubulointerstitial damage that is frequently associated with glomerular lesions in primary glomerulonephritides. The amount of proteinuria and the degree of tubulointerstitial involvement appeared to be better predictors of functional outcome. A correlation between tubular lesions and renal function has been found, referred to some toxicity of proteinuria on tubular cells. There is a significant relationship between the selectivity of proteinuria and the degree of tubulointerstitial damage. Furthermore, the type of peptide fragments eliminated in the urine initiates toxic effects upon the proximal tubule epithelial cells (37).

In patients with ***IgA nephropathy***, fractional excretion of IgG has normalized proportionally to the percentage of glomeruli with segmental sclerosis. Also, the levels of urinary *NGAL, NAG, and Il-6* increase during active disease (38).

In ***membranous nephropathy*** there have been described increased urinary eliminations of *NGAL, L-FABP, NAG, β_2-microglobulin, and IgG*. In ***focal and segmental glomerulosclerosis*** increase the urinary eliminations of *retinol-binding protein*, while in ***minimal change disease*** increase the levels of *NAG* and *urinary TGF beta* (38).

In ***lupus nephropathy***, the levels of urinary ***NGAL, NAG, TGF β, VEGF*** and ***VCAM-1*** correlate with the pathological class of lupus nephropathy (39). *$FOXP_3$* is a regulator of the development and functionality of T cells. The levels of mRNA FOXP3 in the urine are elevated in patients with lupus nephropathy, as compared to patients with systemic lupus erythematosus without renal involvement (40). *TWEAK* (tumor necrosis factor-like weak inducer of apoptosis) is a pro-inflammatory cytokine which increases in the urine of patients with lupus nephropathy (41,42).

In ***ANCA-mediated vasculitides***, increased urinary excretion of *IgM* was associated with renal function decline (38).

Tubulointerstitial nephropathies

Tubulointerstitial lesions are associated to upper urinary tract infections, to acute and chronic pyelonephritis, respectively. Tubular lesions have been evidenced by assessing urinary eliminations of several tubular enzymes. Thus, increased levels of NAG were found as a consequence of tubular cells involvement in tubulointerstitial nephropathies. The assessment of urinary NAG allows an accurate follow-up of the response to antibiotherapy of patients with acute and chronic pyelonephritis (43).

Sherman *et al* have revealed increases in urinary NAG and β_2-microglobulin eliminations in patients with urinary tract infections (44). Due to the fact that the urinary levels of NAG increase in relation to tubular lesions, this enzyme increases only in upper urinary tract infections, but not in lower urinary tract infections. Thus, the eliminations of NAG make the

difference between upper and lower urinary tract infections, respectively (45).

In patients with calcium oxalate renal lithiasis, increased eliminations of tubular enzymes, such as alcaline phosphatase, gamma gluthamyl-transpeptidase, lactic dehydrogenase, and NAG may be used in the diagnosis of the patients prone to developing renal calculi (46).

Renal colic is associated with tubular lesions. Consequently, urinary eliminations of tubular enzymes may be elevated, such as is the case of urinary NAG (47). Tubular lesions may occur due to increased urinary tubular enzymes (48).

According to the observations forwarded by Laterza *et al*, the increase in the pressure of the proximal tubule is produced by the passage of stones, a fact which leads to tubular lesions and subsequent increase in urinary eliminations of tubular enzymes (49). Extracorporeal shock-wave litotripsy is associated with renal lesions, which may be assessed by quantification of urinary enzymes (50).

Proximal tubule dysfunction may occur early in patients with a congenital or surgically aquired single kidney. Tubular lesions are evidenced by increased eliminations of urinary NAG, alpha$_1$-microglobulin, and albuminuria, the latter being now considered a marker of proximal tubule dysfunction, rather than a marker of glomerular lesion (51).

Balkan endemic nephropathy

Balkan endemic nephropathy (BEN) represents a chronic tubulointerstitial nephropathy described amongst renal diseases found in well delimitated areas of Serbia, Bulgaria, and Romania. This disease has a slow and progressive evolution towards chronic renal failure, and finally to end-stage renal disease. Due to the fact that its pathogenesis is incompletely elucidated, an early diagnosis of this disease is very difficult to achieve.

Tubulointerstitial lesions are very important in the course of BEN. Thus, tubular lesions have been evidenced by increased urinary eliminations of NAG, leucine-amino-peptidase, lactic dehydrogenase, and lysosim (52).

Acute kidney injury

Acute kidney injury (AKI), defined as an abrupt decrease in renal function and/or of urinary output, may be induced by various causes, such as infections, toxic and ischaemic mechanisms, hypertension, hereditary and metabolic disorders, autoimmune diseases, and acute rejection of the renal allograft (53).

The incidence of acute kidney injury is increasing to epidemic proportions. Development of AKI leads to excessive morbidity and mortality, prolonged hospitalization, and increased healthcare costs.

Although serum creatinine is tipically used for diagnosis of AKI, it is an insensitive and unreliable biomarker during acute changes in kidney function. The serum creatinine levels do not increase until about half of the kidney function is lost (54,55).

Early detection of AKI requires more reliable and specific biomarkers in order to accurately diagnose acute tubular lesions. Emerging and already established biomarkers are widely used in the early diagnosis of AKI, especially in critically ill patients in the intensive care unit (ICU) (54,56).

The biomarkers indicative of AKI are classified as ***functional markers*** (***enzymatic markers:*** NAG, α/π GST, γ-gluthamyltranspeptidase; ***inflammatory markers:*** Il-18, NGAL), and ***structural markers*** (KIM-1, Na/H-exchanger inform 3, L-FABP). These markers are eliminated in high proportions in the urine of patients with AKI due to tubular lesions.

Furthermore, biomarkers of AKI may be represented by ***low-molecular weight proteins***, normally filtered by the glomeruli and/or metabolised by the normal tubular epithelial cells (cystatin C, α_1-microglobulin, β_2-microglobulin, retinol-binding protein) (57). These biomarkers are useful in differentiating patients with ***established acute renal lesions*** from patients hospitalized for non-renal diseases, chronic kidney disease, and from healthy control subjects (57).

In the emergency departments and in the ICU, several biomarkers, such as NGAL and

NHE3, allow differentiating of cases with established acute renal lesions from increases in serum creatinine due to prerenal azotaemia (58,59).

In clinical practice, early detection of acute renal lesions, within hours of the onset, permits identification of the therapeutic window, in which adequate treatment strategies may improve outcomes, before established lesions and functional modifications occur (57).

Cystatin C has a very high sensitivity in the early detection of renal function modifications, even in mild renal function impairment (60). This biomarker has a diagnostic value superior to serum creatinine in the evaluation of AKI due to its short half-time (61).

Urinary Neutrophil gelatinase-associated lipocalin (NGAL) increases significantly in the proximal tubules and in the first voided urine after AKI through ischaemic mechanisms (62,63). NGAL occurs in the urine before other urinary biomarkers of AKI, relevant for proximal tubule dysfunction, such as NAG and β_2-microglobulin. Therefore, NGAL has been named "renal troponin". Similar aspects have been described in AKI through nephrotoxic mechanisms (64).

The increased levels of urinary NGAL allow differentiating intrinsic AKI from prerenal azotaemia, and also these may serve in stratification of patients with AKI according to the RIFLE criteria (65).

Kidney injury molecule-1 (KIM-1) represents a rapid, sensitive, non-invasive, and reproducible biomarker, used for the early detection of AKI induced by cysplatin and through ischaemic mechanisms (63,66).

N-acetil-beta-D-glucosaminidase (NAG). Increased levels of urinary NAG have been found in tubulointerstitial nephropathies, AKI, drug-induced nephrotoxicity, diabetic nephropathy, and acute renal allograft rejection (63,67).

Liver-type fatty acid-binding protein (L-FABP) increases in the urine before serum BUN and creatinine, in cysplatin and ischaemic mechanisms induced AKI (68). L-FABP also increases in patients with severe sepsis (16).

Exosomal transcription factors may be utilized in the identification of acute renal lesions. Exosomes are microvesicles excreted by normal and injured renal epithelial cells. Urinary exosomes may be released by all segments of the nephron, including podocytes. Exosomes are vesicles of 50-90 nm, created within a cell when a segment of the cell membrane is invaginated and undergoes a process of endocytosis. The internalized membrane segment is fragmented in small vesicles, which may be externalized. Detection of exosomes which contain activator transcription factor 3 (ATF_3) in the urine is indicative of AKI before a rise in serum creatinine (69). These exosomes contain transcription factors which may be activated by various stimuli and may be detected in the urine of patients with AKI (69), and with chronic kidney disease (15,63).

L1 cell adhesion molecule (CD 171) is a membrane glycoprotein which belongs to the immunoglobulin superfamily. The levels of this glycoprotein increase in the urine of patients with acute tubular necrosis, as compared with patients with prerenal azotaemia (16).

Netrins are laminin-like molecules, with a distinctly organised domain. Netrin-1 increases before serum creatinine in patients with AKI induced through ischaemic mechanisms, cysplatin, folic acid, and endotoxins (16).

Aprotinin, also known as a pancreatic tripsin inhibitor, is a protein which increases in the urine of patients with AKI after cardio-pulmonary by-pass (70).

Nephronectin (NPNT), ligand al $alpha_8$ $beta_1$ integrin, is expressed by the uretheral bud during renal morphogenesis. The levels of urinary nephronectin increase in AKI through nephrotoxic mechanisms, reaching its maximal levels in the course of tubular cells regeneration in the onset stage of AKI, and in the recovery period after AKI (71).

Other urinary biomarkers released by the injured proximal tubule cells are ***glutathion-S-transferase, alcaline phosphatase,*** and ***γ gluthamyl-transpeptidase,*** which are indicative of AKI induced by nephrotoxic mechanisms, and of

diabetic nephropathy (16). Also, urinary alpha$_1$-microglobulin and beta$_2$-microglobulin may serve in the diagnosis of AKI (16).

Leucin-aminopeptidase increases in the urine of patients with AKI after exposure to mercury and after iodinated contrast media, such as NN'-diacethyl-3,5diamino-2,4,6-triiodbenzoic acid, utilized for i.v. urography or aortic angiography (72).

Also, drug-induced nephrotoxicity has been evidenced by increased urinary eliminations of NAG (cysplatin) (73), rifampicin (74), aspirin (75), gentamicin (76), and amikacin (47).

It should be stressed that aminoglycosides accumulate and concentrate in the lysosomes within the proximal tubule cells. Lesions in these cells and the cellular organelle are associated with increased urinary NAG eliminations. Mild renal dysfunction due to tubular lesions may be detected early by assessment of NAG (77).

Preeclampsia

High urinary levels of tubular enzymes have been observed during preeclampsia. Manescu *et al* have shown increased urinary eliminations of leucine-aminopeptidase in patients with preeclampsia (primary toxemia of pregnancy). The highest levels of enzymuria were observed in severe forms of preeclampsia, especially in the complicated cases (superimposed eclampsia, uteroplacental apoplexia). The determination of urinary leucine-aminopeptidase may be a relatively accurate test in estimating severity and course of toxemia of pregnancy (78). The cause of high levels of enzymuria may be related to a spastic factor.

An increased cell permeability in the proximal tubule cells, induced either by hypoxia or by humoral factors, such as an increase in urinary oxytokinase excretion can also be an important factor.

Also, increased eliminations of NAG have been reported during preeclampsia. This increase was much higher than that corresponding to the gestational age. This fact is due to the tissue ischaemia that precedes glomerular endotheliosis, but also tubular lesions caused by arteriolar vasoconstriction may have an important role (79).

Concluding remarks

At present time, clinical practice requires advanced studies of plasma and urinary proteomics which should allow identification, selection, and implementation of plasma and urinary biomarkers, useful in the diagnosis of acute and chronic renal diseases, as well as of drug-induced nephrotoxicity. The importance of these biomarkers also resides in their prognostic value and the posibility of their repeated and dinamic assessment, in order to detect early the progression of an acute renal disease to chronic kidney disease, and of the later one to its final stages.

List of abbreviations

AGES – advanced glycation end-products
AKI – acute kidney injury
ANCA – Anti-neutrophil cytoplasmic antibody
ATF3 – activator transcription factor 3
BEN – Balkan endemic nephropathy
BUN – blood urea nitrogen
CKD – chronic kidney disease
α/π GST – α/π Glutathione S-transferase
ICU – Intensive-care unit
IgA – Immunoglobulin A
IgG – Immunoglobulin G
Il-6 – interleukin 6
Il-18 – interleukin 18
KIM-1 – Kidney injury molecule-1
L-FABP – Liver-type fatty acid-binding protein
NAG – N-acethyl-beta-D-glucosaminidase
NGAL – Neutrophile gelatinase-associated lipocalin
NPNT – Nephronectin
TGF beta – Transforming growth factor beta
TWEAK – tumor necrosis factor-like weak inducer of apoptosis
VCAM-1 – Vascular cell adhesion molecule-1
VEGF – Vascular endothelial growth factor

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