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Urinary Biomarkers in Glomerulonephritis

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1. Introduction

A biomarker refers to a biologic, biochemical or molecular event that can be assayed qualitatively and quantitatively by laboratory techniques. The level of biomarkers should correlate with disease pathogenesis or activity. Biomarker discovery for kidney diseases is currently an active area of investigation. Today golden standard for diagnosis and for evaluation of treatment results is kidney biopsy – an invasive test with considerable risks.
Biomarkers have the potential to be useful tools for non invasive evaluation and management of patients suffering from glomerulonephritis. Biomarkers that predict impending disease activity could be used to initiate treatment early, which could minimize the initial insult, allow a reduction in duration and intensity of therapy, improve outcomes and lessen chronic renal injury. Biomarkers that predict response to therapy could be used to choose the most appropriate regimen for an individual patient and biomarkers that reflect disease severity could be used to adjust the intensity of therapy.
Profiles as well as individual markers, with the potential to reduce the use of renal biopsy, improve therapeutic efficacy, and limit toxicity are emerging and this chapter will describe some examples in the context of IgA nephropathy, lupus nephritis, ANCA-associated small vessel vasculitis (ASVV) with renal involvement and focal segmental glomerulosclerosis (FSGS).

2. Proteomics – biomarker patterns

Renal and urinary proteomics are among the most rapidly growing sub disciplines of proteomics applied to biomedical research. There is much interest of nephrologists and renal physiologists in applying proteomics to address clinical and basic questions. Urinary proteome analysis offers opportunities for pattern recognition as well as single biomarker discovery. Urine as a body fluid for clinical analysis is relatively stable, presumably due to the fact that its "stored" for some time in the bladder, hence proteolytic degradation by endogenous proteases may be essentially complete by the time of voiding. Urinary proteins and peptides originate not only from glomerular filtration, but also from tubular secretion, epithelial cells shed from the kidney and urinary tract, secreted exosomes and seminal secretions. Urine is thus a rich source of biomarkers for a wide range of diseases, due to specific changes in its proteome. Commonly used methods for urinary proteome analyses include two-dimensional polyacrylamide gel electrophoresis (2-D PAGE), different types of mass spectrometry, capillary electrophoresis and protein microarrays [Fliser D, Novak J et al 2007; Muller GA, Muller CA & Dihazi 2007].

2.1 Possible clinical applications in glomerulonephrits

2.1.1 Immunoglobulin A (IgA) nephropathy

There are several proteomics studies on IgA nephropathy, showing promising results. A specific urinary polypeptide pattern can distinguish IgA nephropathy from healthy controls with a sensitivity of 100% and specificity of 90%, and from membranous nephropathy with a sensitivity of 77% and a specificity of 100%. In addition, compared with patterns established earlier in minimal change disease, focal segmental glomerulosclerosis and diabetic nephropathy, the pattern of IgA nephropathy had both sensitivity and specificity of 100%. Even most patients in clinical remission with normal clinical testing (dipstick urinalysis and quantitative proteinuria) were correctly classified by the pattern of polypeptides identified. Sequencing of three of the discriminatory polypeptides identified three different fragments of serum albumin. [Haubitz M, Wittke S et al, 2005].

2.1.2 Lupus nephritis

Urinary proteomic profiling was described in lupus nephritis by Mosley et al, 2006. The authors reported that two protein ions had been detected, which could distinguish between active and inactive lupus nephritis with 92% sensitivity and specificity each. The two biomarkers could predict early relapse and remission, but were not further isolated and identified. Zhang et al, 2008, identified three potential low-molecular-weight biomarkers, namely hepcidin, alpha 1 antitrypsin and an N-terminal fragment of albumin. There were two isoforms of hepcidin, 20 and 25 amino acid (aa) long. Hepcidin 20 increased 4 months pre-flare and then slowly returned to baseline by 4 months post-flare. Hepcidin 25 decreased at flare and returned to baseline by 4 months post-flare. There was no correlation between the 20 and 25 aa isoforms. Hepcidin is a LMW peptide hormone that has antimicrobial activity, regulates iron homeostasis, and has been implicated in the pathogenesis of the anemia of chronic inflammation, including that of chronic kidney
Disease [Deicher R, Horl W H 2004]. Urine hepcidin has been shown to increase during inflammation and decline as inflammation resolved. The expression is induced by interleukin-6 (IL-6) and is suppressed by TNF-alpha, cytokines that are implicated in the pathogenesis of SLE [Aringer M, Smolen J S 2005].

2.1.3 ANCA associated small vessel vasculitis

Haubitz et al recently presented one of the first urinary proteomics studies on ANCA associated small vessel vasculitis (ASVV) with renal involvement. Urinary proteome analysis with CE-MS was shown to permit differentiation of patients with active AAV *versus* healthy individuals and patients with other chronic renal diseases. A panel of biomarkers also permits distinguishing between patients with active AAV and patients in remission. Initiation of immunosuppressive treatment results in a change of the pattern from active to inactive disease, correlating with clinically decreasing vasculitis activity and the achievement of remission. The most frequently observed peptides were proteolytic products of hemoglobin. The existence of these fragments is to be expected as microhematuria is a characteristic finding in vasculitis. Remarkably only C- and N-terminal fragments could be defined as biomarkers, whereas fragments from the core of the molecules, although present in urine, showed no significant value as biomarkers. The existence of specific fragments may be a result of the specifically released proteases in ANCA-associated vasculitis after activation of neutrophils by ANCA [Haubitz M, Good D M et al 2009].

2.1.4 Focal segmental glomerulosclerosis

Candiano et al published a proteomics study on idiopathic nephrotic syndrome in 2006, comprising patients suffering from minimal change disease, membranous glomerulonephritis or focal segmental glomerulosclerosis (FSGS). Albumin and alpha 1AT fragments represent the major proteins in urine of patients with nephrotic syndrome, where at least 50 isoforms of these proteins were characterized by proteomics analysis. Most of these isoforms derive from plasma, but a few were formed *in situ* by specific proteolysis. Albumin adducts that harbor both the COOH and NH2 terminal parts of the protein also were detected, suggesting the formation of covalent chemical adducts [Candiano G, Musante L et al 2006]. Two years earlier, Weissinger et al described urinary proteome patterns in healthy subjects, compared to different primary renal diseases. One-hundred seventy-three polypeptides were present in more than 90% of the urine samples obtained from healthy individuals, while 690 polypeptides were present with more than 50% probability. These data permitted the establishment of a "normal" polypeptide pattern in healthy individuals. Polypeptides found in the urine of patients differed significantly from the normal controls. These differences allowed the distinction of specific protein spectra in patients with minimal change disease (MCD), membranous glomerulonephritis (MGN), and focal segmental glomerulosclerosis (FSGS). Abnormal pattern of proteins were found even in urine from patients in clinical remission [Weissinger E M, Wittke S et al 2004].

3. Individual biomarkers

3.1 Immunoglobulin A (IgA) nephropathy

Urinary concentration of several cytokines involved in proliferation and repair has been evaluated as potential biomarkers of histopathological changes and as predictors of long-term prognosis in IgA nephropathy. Urinary IL-6 has been shown to predict long term renal outcome in IgA nephropathy [Harada K, Akai Y et al 2002]. The excretion of IL-6 and epidermal growth factor (EGF) has been correlated with degree of tubulointerstitial damage, with the urinary IL-6/EGF ratio proposed as a marker for progression of the renal damage [Ranieri E, Gesualdo L et al 1996]. Other potential markers that have been evaluated include urinary alpha 1 antitrypsin and heparan sulfate [Mitsuhashi H, Tsukada Y et al 1993]. Urine N-acetyl-alpha-D-glucosaminidase (NAG) levels are measured in some clinics. NAG is a lysosomal enzyme abundant in lesions of proximal tubular damage in patients with nephrotic syndrome, glomerulonephritis and diabetic nephropathy. Nonetheless, the sensitivity and specificity of this biomarker for IgAN is not ideal. In patients characterized with tubulointerstitial lesion, urinary NAG levels correlated well with the extent of tubulointerstitial changes. In patients characterized with primary glomerular lesion and accompanied tubulointerstitial changes such as IgAN, the elevated urinary NAG levels often lag the morphologic changes due to tubulointerstitial injury [Bazzi C, Petoni V et al 2002]. Ding et al presented a study in 2007, claiming that urinary NGAL level holds promise as a noninvasive marker, more sensitive and specific than NAG, for early detection of sub-microscopic tubulointerstitial injury of IgAN [Ding H, Yani H et al 2007]. Urinary IgG and IgA correlated with glomerular filtration rate and grading of histological features and was significantly elevated compared to healthy controls [Halling S F E, Söderberg M P & Berg U B 2005]. Despite these promising reports of differential presence of proteins and protein complexes, none of the tests has so far been developed into a clinically useful assay. Very recently, Peters et al published a study demonstrating high urinary levels of kidney injury

molecule 1 (KIM-1) as an independent predictor of end stage renal disease in patients with IgA nephropathy [Peters H P, Waanders F et al 2011].

3.2 Lupus nephritis

Current laboratory markers, such as proteinuria, urine protein-to-creatinine ratio, creatinine clearance, anti-dsDNA and complement levels are unsatisfactory. They lack sensitivity and specificity for differentiating renal activity and damage in lupus nephritis. There are many candidate biomarkers in lupus nephritis. In this chapter, we have chosen to describe some of the most promising ones.

3.2.1 Monocyte chemoattractant protein 1

Monocyte chemoattractant protein 1 (MCP-1) is a leukocyte chemotactic factor, involved in mediating inflammation and injury in lupus nephritis. MCP-1 drives fibrosis both indirectly via macrophages, but also through direct induction of a fibrotic response in glomerular mesangial cells [Tesch G H 2008]. The urinary MCP-1 level is elevated in active lupus nephritis, compared to inactive disease and healthy controls, and reduced after immunosuppressive treatment [Wada T, Segawa C et al 1996]. In a longitudinal follow up, urinary MCP-1 increased 2-4 months before renal flares and remained high for at least 4 months after treatment of flares. In patients who improved clinically, MCP-1 levels fell to control levels, whereas in treatment refractory patients, the levels remained high [Rovin B H, Song D J et al 2005]. Thus MCP-1 is a very promising biomarker in lupus nephritis and possibly also a future therapeutic target.

3.2.2 Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is constitutively expressed at low levels in the kidneys, but up regulated following acute renal injury and various insults such as inflammation, ischemia and infection and considered as a good biomarker for acute kidney injury, with high sensitivity and specificity [Bolignano D, Donato V et al 2008]. NGAL In lupus nephritis, urinary levels of NGAL has been found to differentiate between patients with or without active renal disease. NGAL correlates more strongly with histological activity scores than chronicity scores on renal biopsies. Significant correlation has been seen with urine protein-to-creatinine ratios but not with proteinuria, serum creatinine level or conventional markers such as anti-dsDNA and complement levels. In longitudinal studies, NGAL was found to increase up to 3 months before renal flare and is considered to be a very promising biomarker in lupus nephritis [Hinze C H, Suzuki M et al 2008].

3.2.3 Tumor Necrosis Factor-Like Inducer of Apoptosis

Tumor necrosis factor-like inducer of apoptosis (TWEAK) is a multifunctional cytokine, involved in up regulation of pro inflammatory mediators and induction of cell death and apoptosis. TWEAK expression is dramatically increased in the context of inflammation and injury and its expression is found to be dysregulated in chronic inflammatory states [Winkles J A 2008]. Stimulation of kidney cells with TWEAK induces expression of chemokines and inflammatory mediators, such as MCP-1, RANTES, IP-10, VCAM-1 and ICAM-1 – which have all been suggested as biomarkers in SLE. Urinary TWEAK levels were significantly higher in patients with active nephritis, compared to inactive. Urinary TWEAK also correlated with renal SLE activity scores, anti-dsDNA and complement levels, but there

was on the other hand no correlation with proteinuria – suggesting that the increased levels in urine was not merely due to glomerular damage. The urinary TWEAK levels peaked at the time of flare, with an increasing trend before and a decreasing trend after flares. Unfortunately, the small rise in uTWEAK prior to the disease flare does not appear to have any predictive value [Gaipl U S, Voll R E et al 2005]. Urinary TWEAK did not discriminate between different LN histological classes. This is a common problem in LN biomarker studies. The problem probably relates to the small number of subjects studied who are then sub grouped into a number of histological classes, the inherent sampling error associated with renal biopsy, and the lack of a clear system to assess inflammatory disease activity at the tissue level.

3.3 ANCA associated small vessel vasculitis

Previous studies have shown that the renal function at diagnosis is a strong predictor not only for renal survival but also for patient survival in ASVV. Other factors have also been reported to predict outcome in ASVV, such as severity of the disease at diagnosis, treatment related infections, alpha 1 antitrypsin deficiency, high levels of PR3-ANCA measured by capture ELISA and low levels of thrombocytes. However these findings have usually not been confirmed in repeated investigations. Proteinuria, severe interstitial fibrosis and glomerulosclerosis, which are known to predict outcome in chronic proteinuric glomerulonephritides have also been found to be important risk factors for development of renal failure in ASVV [Pallan L, Savage CO & Harper L 2009]. The need of better non invasive prognostic markers is significant.

3.3.1 Monocyte chemoattractant protein 1

Indirectly, by macrophage recruitment, and also via direct induction of a fibrotic response in glomerular mesangial cells – MCP-1 has the potential to drive the process of renal fibrosis [Tesch G H 2008]. Urinary excretion of MCP-1 is increased in patients with ASVV. The degree of excretion correlates significantly with patient outcome, considering critical damage or death. The association with poor prognosis was stronger for U-MCP-1 than for conventional prognostic markers like CRP, BVAS (Birmingham vasculitis activity score), and ANCA, as well as compared to candidate markers like U- IgM and U-IL-8 [Ohlsson S, Bakoush O et al 2009]. Urinary MCP-1 is considered very promising biomarker in ASVV. A longitudinal study for validation of these results is ongoing.

3.3.2 IgM

In other glomerulonephritides, not associated with vasculitis, elevated urine excretion of high molecular weight proteins, e. g. IgM, has been found to be a better predictor of renal outcome than the degree of albuminuria. In ASVV, urinary levels of IgM was found to be a better independent predictor of renal survival than serum creatinine at diagnosis and, in addition to age, it was an important predictor for patient survival. Patients with low urinary IgM excretion maintained their kidney function despite a high degree of albuminuria, and patients with high urine IgM excretion were more likely to develop ESRD [Bakoush O, Segelmark M et al 2006]. The authors of this study recommend routine measurement of urine IgM concentrations at diagnosis in patients with ANCA-associated small vessel vasculitis, as a relatively cheap, non-invasive and early prognostic marker.

3.3.3 FSGS

The glomerular microenvironment is influenced by circulating growth factors that are filtered from the blood stream and pass the glomerular filtration barrier. The role of IGF-binding proteins (IGFBPs) has been studied in two diseases that concern podocytes. The glomerular expression and urinary excretion of IGFBP-1, -2, and -3 were studied in patients with focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD). It was found that patients with active FSGS excrete high amounts of IGFBP-1 and -3. In human podocytes, we can induce mRNA expression of IGFBP-3 in response to TGF-β and in human microvascular endothelial cells expression of IGFBP-1 and -3 in response to TGF-β and Bradykinin. The conclusion was that the local expression of IGFBPs in podocytes and endothelial cells might contribute to the pathogenesis of glomerular disease and that IGFBP-1 and -3 are potential non-invasive markers of FSGS, differentiating against MCD [Worthmann K, Peters I et al 2010].

4. Summary

Urinary proteomics has great potential in biomarker discovery in kidney diseases. So far we have partially achieved the goals to better understand the biology and physiology of the kidney, and to unravel pathogenic mechanisms and /or pathophysiology of kidney disorders.

Biomarker	**Diagnosis/Reference**
Hepcidin	Lupus/Zhang et al 2008
Alpha-1-antitrypsin	Lupus/Zhang et al 2008 IgAN/Mitsuhashi et al 1993
Albumin, N-terminal	Lupus/Zhang et al 2008
Albumin fragments	IgAN/Haubitz et al 2005
Hemoglobulin, N- and C-terminal parts	ASVV/Haubitz et al 2005
IL-6	IgAN/Harada et al 2002
EGF	IgAN/Raniere et al 1996
Heparansulfate	IgAN/Mitsuhashi et al 1993
NAG	IgAN/Bazzi et al 2002
NGAL	IgAN/Ding et al 2007 Lupus/Hinze et al 2008
IgG	IgAN/Halling et al 2005
IgA	IgAN/Halling et al 2005
IgM	ASVV/Bakoush et al 2006
KIM-1	IgAN/Peters et al 2011
MCP-1	Lupus/Wada et al 1996, Rovin et al 2005 ASVV/Ohlsson et al 2009
TWEAK	Lupus/Gaipl et al 2005
IGFBP-1, -3	FSGS/Worthmann et al 2010

Table I. Urinary biomarkers in glomerulonephritis. IgAN: IgA-nephritis, IL-6: interleukin 6, EGF: epidermal growth factor, NAG: N-acetyl-alpha-D-glucosaminidase, NGAL: neutrophil gelatinase associated lipocalin, KIM-1: kidney injury molecule, MCP-1: monocyte chemoattactant protein 1, TWEAK: Tumor necrosis factor-like inducer of apoptosis, IGFBP: insulin-like growth factor binding protein

For biomarker discovery, although a large number of biomarker candidates have been identified, they are neither fully validated in a large cohort, nor ready for routine clinical practice at present. NGAL and MCP-1 are both extremely promising urinary biomarkers. Whereas NGAL seems to be more of a marker of acute kidney injury, the prognostic value of MCP-1 most likely comes from this protein's role in driving the process of fibrosis and scarring. In experimental glomerulonephritis, there is increased glomerular synthesis of MCP-1, and systemic administration of an anti-MCP-1 antibody has been demonstrated to reduce the severity of acute glomerulonephritis as well as subsequent scarring, implying that MCP-1 could be a possible therapeutic target also in man [Wada T, Yokoyama H et al 1996].

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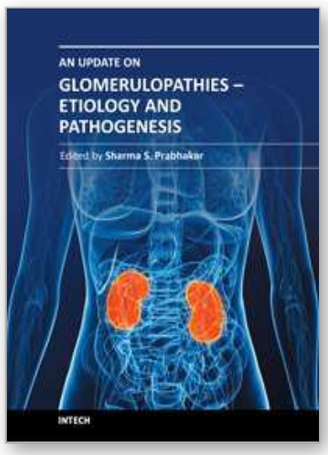

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