Research Article

Urinary β2-Microglobulin Is a Good Indicator of Proximal Tubule Injury: A Correlative Study with Renal Biopsies

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Received 26 August 2014; Revised 22 October 2014; Accepted 5 November 2014; Published 20 November 2014

Academic Editor: Rafael Noal Moresco

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Objective. After filtration through glomeruli, β2-microglobulin is reabsorbed in proximal tubules. Increased urinary β2-microglobulin indicates proximal tubule injury and measurement of β2-microglobulin in urine is useful to determine the source of renal injury. Kidney injury molecule-1 (KIM-1) has been characterized as a selective proximal tubule injury marker. This study was designed to evaluate the correlation of urinary β2-microglobulin concentration and KIM-1 expression as evidence of proximal tubule injury. Methods. Between 2009 and 2012, 46 patients with urine β2-microglobulin (RenalVysion) had follow-up kidney biopsy. Diagnoses included glomerular and tubule-interstitial disease. Immunohistochemical staining for KIM-1 was performed and the intensity was graded from 0 to 3+. Linear regression analysis was applied to correlate the values of urinary β2-microglobulin and KIM-1 staining scores. Results. Thirty patients had elevated urinary β2-microglobulin. KIM-1 staining was positive in 35 kidney biopsies. There was a significant correlation between urinary β2-microglobulin and KIM-1 staining (P < 0.05). Sensitivity was 86.6%, specificity was 43.7%, positive predictive value was 74.2%, and negative predictive value was 63.6%. Conclusion. Increased urinary β2-microglobulin is significantly correlated with KIM-1 staining in injured proximal tubules. Measurement of urine β2-microglobulin is a sensitive assay for proximal tubule injury.

1. Introduction

Acute kidney injury is a common clinical syndrome that is characterized by a rapid decline in kidney function, often triggered by glomerular disease and/or tubulointerstitial disease and associated with high morbidity and mortality [1–4]. In addition to serum creatinine, β2-microglobulin is a biomarker that can be used to determine underlying causes of acute kidney injury [5]. Serum β2-microglobulin derives from cellular membrane turnover [6], since β2-microglobulin forms the invariant light chain portion of major histocompatibility complex (MHC) class I in membranes of all cells [7–10]. As a single-chain small polypeptide (MW = 11.8 kDa), β2-microglobulin is filtered almost completely through the glomeruli of the healthy kidney [11, 12] and then reabsorbed by the renal proximal tubules. Only a small amount of β2-microglobulin can be detected in the urine under normal physiological conditions. Therefore, levels of serum and urinary β2-microglobulin reflect the functions of glomeruli and proximal tubules [13]. In patients with acute kidney injury, an increase in serum creatinine, together with an increase in urinary β2-microglobulin, strongly suggests proximal tubule injury. On the other hand, an increase in serum creatinine with elevated serum β2-microglobulin is seen in patients with decrease in glomerular filtration rate [14]. Elevated urinary β2-microglobulin was associated with tubular injury caused by viral infection, ischemia, and toxicity from medications or heavy metals [15, 16].

Measurement of urinary β2-microglobulin is convenient and has been applied in routine clinical practice (RenalVysion Bostwick Laboratories, Uniondale, NY) to evaluate
the tubular function [17]. Using immunohistochemical staining for CD133 in kidney biopsies, we demonstrated that urinary β2-microglobulin is a sensitive indicator for tubular injury [5]. However, a direct correlation between urinary β2-microglobulin and proximal tubule injury has not yet been fully established due to lack of a specific proximal tubule injury marker.

Recently, kidney injury molecule-1 (KIM-1) was shown to be a biomarker for proximal tubule injury [18–20]. KIM-1 is a type 1 cell membrane glycoprotein comprised of extracellular, transmembrane and intracellular domains [21, 22]. KIM-1 is undetectable in the healthy kidney [19]. With different forms of kidney injury, mRNA and protein levels of KIM-1 are upregulated and expressed [20, 23, 24] in injured tubules [23, 25–27]. KIM-1 binds to surface-specific epitopes on the apototic bodies and cellular debris derived from injured tubular cells, facilitating macrophages to engulf dying cells [19]. In addition, the extracellular domain of KIM-1 can be cleaved by metalloproteinases into a soluble shedded part and short membrane bound fragments that are released into urine. Therefore, the presence of KIM-1 in tubular epithelium and/or urine indicates tubule injury. Moreover, the expression of KIM-1 in injured tubule cells is limited to the proximal tubular cells [25]. Using immunohistochemistry, KIM-1 staining in kidney tissue has been shown to accurately detect proximal tubular injury associated with ischemic and toxic type of tubular injury, allograft rejection in renal transplantation, and acute pyelonephritis [20, 26, 28].

The present study was designed to examine the correlation between increase in urinary β2-microglobulin and proximal tubule injury assessed by KIM-1 staining in kidney biopsies.

2. Materials and Methods

Between January 2009 and December 2012, a total of 5494 patients had urinary β2-microglobulin measurements by RenalVysion analysis (Bostwick Laboratories). Among these, fifty-six patients had follow-up renal biopsies. Nine renal biopsies either contained less than 10 glomeruli per histological section or had insufficient tissue to perform immunohistochemical staining and were excluded from the present study. One biopsy showed high background staining and was also excluded. The remaining forty-six biopsies met selection criteria and were included in the present study.

Urine collection followed the instruction of RenalVysion. Briefly, 10 mL fresh urine was collected from each patient and urine pH was adjusted to pH 6–8 with 1 M NaOH. The specimen was delivered to lab by overnight shipping and urine pH was adjusted to pH 6–8 with 1M NaOH. The presence of 2-microglobulin was measured next day. The 2-microglobulin level and intensity of KIM-1 staining. Data were also stratified according to urinary 2-microglobulin level as normal (<300 μg/L) versus increased to KIM-1 staining (positive or negative) and evaluated by 2 × 2 contingency table (Table 2). The sensitivity, specificity, predictive value for positive result, and predictive value for negative result were calculated as follows:

\[
\text{sensitivity} = \frac{\text{true positive}}{\text{true positive + false negative}};
\]
\[
\text{specificity} = \frac{\text{true negative}}{\text{true negative + false positive}};
\]
\[
\text{predictive value for positive result} = \frac{\text{true positive}}{\text{true positive + false positive}};
\]
\[
\text{predictive value for negative result} = \frac{\text{true negative}}{\text{true negative + false negative}};
\]

The age of the patients was expressed as mean ± SD.

3. Results

Among 5494 patients with urinary β2-microglobulin measurement, renal biopsy was obtained out in 56 patients
(56/5494, 1.0%). Among these, 46 biopsies met the selection criteria and were included in present study. Thirty patients had increases in urinary β2-microglobulin; it was in normal range in the remaining 16 patients. The demographic details for 35 patients (M : F = 22 : 13) with positive KIM-1 staining in proximal tubules are shown in Table 1. The age of patients at the time of biopsy was 54.9 ± 10.7 years ranging from 16.0 to 87.0 years. The majority of renal biopsies were performed in native kidneys. Two biopsies were from renal transplant patients. A majority of renal biopsies showed glomerular disease. Nine patients had combined glomerular and tubulointerstitial involvement. Glomerular diseases included membranous nephropathy, antineutrophil cytoplasmic antibody- (ANCA-) associated glomerulonephritis, diabetic nephropathy, focal and segmental glomerulosclerosis, IgA nephropathy, and lupus nephritis. Four patients had diabetic nephropathy, focal and segmental glomerulosclerosis, and tubulointerstitial involvement. Glomerular diseases contributed to elevation of serum creatinine. Measurement of urinary β2-microglobulin was a reliable assay to detect proximal tubule injury. Therefore, in patients with acute kidney injury with increase in serum creatinine, measurement of urinary β2-microglobulin is also helpful to identify the underlying tubular dysfunction, that is, proximal tubule injury.

4. Discussion

We found that increased urinary β2-microglobulin was significantly correlated with KIM-1 staining in proximal tubules, indicating that urinary β2-microglobulin is a sensitive (sensitivity 86.6%) assay for detecting tubular injury. Further, because KIM-1 is a selective proximal tubule injury marker, the present study also demonstrated that measurement of urinary β2-microglobulin was a reliable assay to detect proximal tubule injury. Therefore, in patients with acute kidney injury with increase in serum creatinine, measurement of urinary β2-microglobulin is also helpful to identify the underlying tubular dysfunction, that is, proximal tubule injury.

Acute tubular injury is a common clinical diagnosis. In a patient with classic clinical presentations such as hypotension together with a rapid rising of serum creatinine, the diagnosis of severe tubular injury (acute tubular necrosis) can be made and does not require kidney biopsy to initiate treatment. However, the diagnosis of glomerular disease accompanied by tubular injury is not easy to establish, as both may contribute to elevated serum creatinine. As shown in Table 1, the majority of kidney biopsies showed glomerular disease. Tubular injury was the secondary diagnosis in 5/35 patients but other evidence of tubular injury such as tubular casts and an increase in tubular cells by urine analysis was found in 22/35 patients. Moreover, 2 of 4 patients with secondary diagnosis of acute interstitial nephritis showed tubulitis, a feature associated with tubular injury. These findings indicate that glomerular diseases associated with varying degree of tubular injury could be missed in renal biopsies due to sampling. In a prior study, using CD133 staining in injured tubular epithelium, it was demonstrated that urinary β2-microglobulin was a sensitive indicator for tubular injury [5]. As a progenitor marker, CD133 positive cells were scattered along the tubular epithelium. Thus, confluent CD133 staining is required to diagnose tubular injury. In addition, CD133 positive cells are present not only in proximal tubular cells but also in distal tubular cells and/or atrophic tubules. Therefore, a careful morphological correlation is needed to exclude false positive staining. By comparison, KIM-1 is a selective proximal tubule injury marker that only presents in patients with proximal tubule injury [18–20]. No staining for KIM-1 was in healthy tubular epithelium. No distal tubular cell or atrophic tubular cell staining was identified. Therefore, KIM-1 is a more specific marker than CD133 for detecting proximal tubular injury. In the present study, KIM-1 was able to detect patients with mild, focal tubular injury evidenced by urine analysis as an increase in number of tubular cells; some patients presented with normal levels of serum creatinine (Table 1). This was also supported with the finding in the present study that more than half of KIM-1 staining score was weakly positive (1+). These findings highlight that KIM-1 is a sensitive marker for proximal tubular injury. A good correlation of urinary β2-microglobulin and KIM-1 staining...
### Table 1: Clinical indices, diagnosis, concentration of β2-microglobulin, serum creatinine, and urine analysis.

| Age (year) | Gender | Diagnosis                                          | β2-microglobulin (µg/L) | KIM score | Serum creatinine (mg/dL) | Urine analysis                  |
|------------|--------|----------------------------------------------------|-------------------------|-----------|--------------------------|---------------------------------|
| 53         | F      | IgA nephropathy                                    | <0.21                   | 0.5       | 0.9                      | Hematuria                       |
| 72         | M      | Membranous nephropathy                             | <0.21                   | 1.5       | 2.4                      | Tubular cells, hematuria        |
| 59         | F      | Diabetic nephropathy                               | <0.21                   | 1.0       | 1.51                     | ↑ Tubular cells                 |
| 51         | F      | Focal, segmental glomerulosclerosis                | <0.21                   | 1.0       | 1.1                      | Hematuria                       |
| 46         | M      | Diabetic nephropathy, IgA nephropathy              | <0.21                   | 2.0       | 2.5                      | Tubular cells, hematuria        |
| 37         | M      | Lupus nephritis                                    | <0.21                   | 1.5       | 3.2                      | Tubular cells, hematuria        |
| 72         | F      | Acute interstitial nephritis, IgA nephropathy      | <0.21                   | 2.0       | 2.3                      | Hematuria                       |
| 69         | M      | Membranous nephropathy                             | 0.28                    | 1.0       | 0.99                     | ↑ Tubular cells                 |
| 87         | M      | IgA nephropathy, acute interstitial nephritis      | 0.29                    | 2.0       | 3.2                      | ↑ Tubular cells                 |
| 50         | M      | Lupus nephritis, tubular injury (toxic)            | 0.31                    | 3.0       | 0.64                     | ↑ Tubular cells                 |
| 83         | M      | Diabetic nephropathy, tubular injury               | 0.33                    | 1.0       | 1.00                     |                                |
| 53         | F      | Focal, segmental glomerulosclerosis                | 0.47                    | 1.0       | 2.40                     | ↑ Tubular cells                 |
| 60         | M      | IgA nephropathy, tubular injury                    | 0.49                    | 2.0       | 5.00                     | ↑ Tubular cells, hematuria      |
| 29         | M      | Renal transplantation, tubular injury              | 0.53                    | 2.0       | 4.50                     | ↑ Tubular cells, hematuria      |
| 35         | M      | IgA nephropathy                                    | 0.54                    | 2.0       | 2.90                     | ↑ Tubular cells, hematuria      |
| 49         | M      | Lupus nephritis                                    | 0.63                    | 3.0       | 1.03                     | ↑ Tubular cells                 |
| 68         | M      | Focal, segmental glomerulosclerosis                | 0.69                    | 1.0       | 1.15                     | Hematuria                       |
| 44         | F      | Focal, segmental glomerulosclerosis                | 1.15                    | 1.0       | 1.10                     | ↑ Tubular cells, hematuria      |
| 16         | F      | Focal, segmental glomerulosclerosis                | 1.60                    | 3.0       | 2.00                     | ↑ Tubular cells, hematuria      |
| 52         | F      | Granuloma                                           | 1.89                    | 2.0       | 0.70                     | ↑ Tubular cells                 |
| 50         | M      | IgA nephropathy                                    | 1.89                    | 2.0       | 0.83                     |                                |
| 20         | M      | Normal                                              | 4.52                    | 1.0       | 3.26                     | ↑ Tubular cells                 |
| 47         | M      | Focal, segmental glomerulosclerosis                | 5.36                    | 2.0       | 1.18                     | ↑ Tubular cells, hematuria      |
| 47         | M      | Renal transplantation                               | 5.44                    | 2.0       | 1.19                     | Hematuria                       |
| 74         | M      | Focal, segmental glomerulosclerosis                | 6.23                    | 3.0       | 1.50                     | Granular casts                  |
| 63         | F      | Focal, segmental glomerulosclerosis                | 7.19                    | 1.0       | 4.50                     | ↑ Tubular cells, hematuria      |
| 38         | M      | Diabetic nephropathy                               | 7.87                    | 2.0       | 3.00                     | Granular casts                  |
| 77         | F      | ANCA-associated glomerulonephritis                 | 9.23                    | 3.0       | 2.90                     |                                |
| 73         | M      | ANCA-associated glomerulonephritis                 | 12.9                    | 1.5       | 2.30                     |                                |
| 63         | M      | Diabetic nephropathy, tubular injury (toxic)       | 16.1                    | 1.0       | 6.00                     | ↑ Tubular cells                 |
| 42         | M      | Focal, segmental glomerulosclerosis                | 29.8                    | 1.0       | 1.70                     | Neutrophils                     |
| 62         | F      | Focal, segmental glomerulosclerosis                | 35.9                    | 3.0       | 7.10                     | ↑ Tubular cells                 |
| 68         | F      | Focal, segmental glomerulosclerosis                | 46.3                    | 2.0       | 2.50                     | ↑ Tubular cells                 |
| 53         | F      | Acute interstitial nephritis                        | 47.2                    | 1.0       | 5.60                     | ↑ Tubular cells                 |
| 60         | M      | Acute interstitial nephritis                        | 79.8                    | 2.0       | 4.50                     | ↑ Tubular cells                 |
Figure 1: (a) Normal proximal tubules with back to back proximal tubules and abundant cytoplasm (H&E 40 × 10). (b) In addition to flattening and simplification of tubular epithelium, injured proximal tubules show granular cytoplasmic and membrane staining for KIM-1 (20 × 10). (c) Ischemia type of tubular injury shows flattening and simplification of tubular epithelium (H&E 40 × 10). (d) In addition to flattened tubular epithelium, toxic type of tubular injury reveals vacuoles in cytoplasm (H&E 40 × 10).

R = 0.293, P < 0.05

Similar to CD133 staining, KIM-1 was also able to identify two major types of tubular injury: ischemic and toxic type (Figures 1(c) and 1(d)). As shown in Table 2, tubular injury was an additional diagnosis included in 5 of 26 biopsies (25%) (Table 1), and all showed positive KIM-1 staining in proximal tubules.

Using KIM-1 staining as a proximal tubule injury marker in the present study, specificity was lower than the prior study that used CD133 staining [5]. Nine patients, rather than six patients with normal urinary β2-microglobulin, presented with positive KIM-1 staining, which were considered false positive. With low specificity, clinical interpretation of elevated urinary β2-microglobulin should be closely correlated with clinical history, (e.g., history of hypotension, recent history of medications use, etc.) and clinical presentation, including value of serum creatinine, as well as urine cytological findings. The diagnosis of tubular injury with RenalVysion was made not only based on the elevation of urinary β2-microglobulin and serum creatinine but also combined with morphological findings of tubular casts and the number of sloughed tubular epithelial cells in urine analysis.

RenalVysion is a urine-based analysis that combines urine chemistry and cytology to detect glomerular disease and tubular injury. Normal range of urinary β2-microglobulin was set between 230 µg/L and 300 µg/L [29]. Elevation of urinary β2-microglobulin over 300 µg/L was considered to be abnormal by RenalVysion. Therefore, nine patients with

(R value of 0.293) indicates that measurement of urinary β2-microglobulin is a reliable assay for proximal tubule injury.
urnary $\beta_2$-microglobulin $<300\mu g/L$ and positive KIM-1 staining in biopsies were considered to be false positive. However, the actual values of urinary $\beta_2$-microglobulin in 2 patients were marginally high in 280 $\mu g/L$ and 290 $\mu g/L$. The remaining 7 patients were found to have levels less than 210 $\mu g/L$, which is the measurement threshold of the assay. Because the confidence interval at the 95% range in lower end was 2.868 in present study, the normal range of urinary $\beta_2$-microglobulin applied in RenalVysion should be reconsidered to be 2.868 $\mu g/L$. If so, the patient with urinary $\beta_2$-microglobulin of 290 $\mu g/L$ should be considered as abnormal and belongs to true positive for KIM-1 staining. Therefore, corrected sensitivity is 87.1%, specificity is 46.6%, positive predictive value is 77.1%, and negative predictive value is 63.6%.

Our study has multiple limitations. Only a small number of patients had follow-up renal biopsies after RenalVysion (56/5494, 1.0%), raising concern for selection and ascertainment biases. As shown in Table 1, these patients had glomerular disease and/or tubular-interstitial disease. No severe tubular injury as the single diagnosis was seen. The reason for this might be that renal biopsy is usually avoided in patients with a clear clinical diagnosis of severe tubular injury. A larger study cohort involving patients with severe tubular injury is needed to better correlate renal histopathology and immunohistochemistry. Owing to limited sampling by biopsies, a focal tubular lesion might be missed in kidney biopsies chosen in present study. The retrospective nature of the study represents an additional limitation.

In summary, measurement of urinary $\beta_2$-microglobulin is a sensitive assay to screen patients with proximal tubule injury. Our data indicate a correlation of urinary $\beta_2$-microglobulin with results of immunohistochemical staining of KIM-1 in renal biopsy and consequently with proximal tubular injury.

### Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

### Acknowledgments

The authors would like to acknowledge the technical support from Betty Ballester and Etnita Nuñez in their professional preparation of histological slides. This work was presented at the annual meeting of the American Society of Nephrology, Philadelphia, PA, USA, November 2014.

### Table 2: Correlation of urinary $\beta_2$-microglobulin and KIM-1 staining.

| $\beta_2$-microglobulin | KIM-1 (+) | KIM-1 (-) |
|-------------------------|----------|-----------|
| increase (30)            | 26       | 4         |
| normal (16)             | 9        | 7         |

### References

[1] G. M. Chertow, E. Burdick, M. Honour, J. V. Bonventre, and D. W. Bates, “Acute kidney injury, mortality, length of stay, and costs in hospitalized patients,” *Journal of the American Society of Nephrology*, vol. 16, no. 11, pp. 3365–3370, 2005.

[2] J. L. Xue, F. Daniels, R. A. Star et al., “Incidence and mortality of acute renal failure in medicare beneficiaries, 1992 to 2001,” *Journal of the American Society of Nephrology*, vol. 17, no. 4, pp. 1135–1142, 2006.

[3] M. T. James, R. Wald, C. M. Bell et al., “Weekend hospital admission, acute kidney injury, and mortality,” *Journal of the American Society of Nephrology*, vol. 21, no. 5, pp. 845–851, 2010.

[4] J.-P. Lafrance and D. R. Miller, “Acute kidney injury associates with increased long-term mortality,” *Journal of the American Society of Nephrology*, vol. 21, no. 2, pp. 345–352, 2010.

[5] X. Zeng, D. Hossain, D. Bostwick, G. Herrera, B. Ballester, and P. L. Zhang, “Urinary $\beta_2$-microglobulin is a sensitive indicator for renal tubular injury,” *Scholarena Case Reports*, vol. 1, no. 1, pp. 103–108, 2014.

[6] M. D. Poulik and R. A. Reisfeld, “Beta2-microglobulins,” *Contemporary Topics in Molecular Immunology*, vol. 4, pp. 157–204, 1975.

[7] P. J. Bjorkman, M. A. Saper, B. Samraoui, W. S. Bennett, J. L. Strominger, and D. C. Wiley, “Structure of the human class I histocompatibility antigen, HLA-A2,” *Nature*, vol. 329, no. 6139, pp. 506–512, 1987.

[8] M. A. Saper, P. J. Bjorkman, and D. C. Wiley, “Refined structure of the human histocompatibility antigen HLA-A2 at 2.6 A resolution,” *Journal of Molecular Biology*, vol. 219, no. 2, pp. 277–319, 1991.

[9] E. J. Collins, D. N. Garboczi, M. N. Karpusas, and D. C. Wiley, “The three-dimensional structure of a class I major histocompatibility complex molecule missing the alpha 3 domain of the heavy chain,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 92, no. 4, pp. 1218–1221, 1995.

[10] J. B. Lindblom, L. Oestberg, and P. A. Peterson, “$\beta_2$-Microglobulin on the cell surface. Relationship to HLA antigens and the mixed leucocyte culture reaction,” *Tissue Antigens*, vol. 4, no. 2, pp. 186–196, 1974.

[11] U. Ravnskov, “Letter: serum beta2-microglobulin and glomerular function,” *The New England Journal of Medicine*, vol. 294, no. 11, p. 611, 1976.

[12] C. Bianchi, C. Donadio, G. Tramonti, C. Consani, P. Lorusso, and G. Rossi, “Reappraisal of serum $\beta_2$-microglobulin as marker of GFR,” *Renal Failure*, vol. 23, no. 3–4, pp. 419–429, 2001.

[13] B. Bussolati and G. Camussi, “New insights into the renal progenitor cells and kidney diseases by studying CD133,” *Advances in Experimental Medicine and Biology*, vol. 777, pp. 113–123, 2013.

[14] C. Donadio, “Serum and urinary markers of early impairment of GFR in chronic kidney disease patients: diagnostic accuracy of urinary $\beta$-trace protein,” *The American Journal of Physiology—Renal Physiology*, vol. 299, no. 6, pp. F1407–F1423, 2010.

[15] B. Bogdanikowa, “$\beta_2$ microglobulin—its properties, occurrence and diagnostic usefulness,” *Postepy Higieny Medycyny Doswiadczalnej*, vol. 35, no. 5, pp. 495–510, 1981.

[16] N. Häring, H. S. Mähr, M. Mündle, R. Strohal, and K. Lhotta, “Early detection of renal damage caused by fumaric acid ester therapy by determination of urinary $\beta_2$-microglobulin,” *British Journal of Dermatology*, vol. 164, no. 3, pp. 648–651, 2011.
[17] R. J. Trof, F. di Maggio, J. Leemreis, and A. B. J. Groeneveld, "Biomarkers of acute renal injury and renal failure," Shock, vol. 26, no. 3, pp. 245–253, 2006.
[18] J. V. Bonventre and L. Yang, "Kidney injury molecule-1," Current Opinion in Critical Care, vol. 16, no. 6, pp. 556–561, 2010.
[19] F. Waanders, M. M. van Timmeren, C. A. Stegeman, S. J. L. Bakker, and H. van Goor, "Kidney injury molecule-1 in renal disease," The Journal of Pathology, vol. 220, no. 1, pp. 7–16, 2010.
[20] W. K. Han, V. Bailly, R. Abichandani, R. Thadhani, and J. V. Bonventre, "Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury," Kidney International, vol. 62, no. 1, pp. 237–244, 2002.
[21] Z. Zhang, B. D. Humphreys, and J. V. Bonventre, "Shedding of the urinary biomarker kidney injury molecule-1 (KIM-1) is regulated by MAP kinases and juxtamembrane region," Journal of the American Society of Nephrology, vol. 18, no. 10, pp. 2704–2714, 2007.
[22] V. Bailly, Z. Zhang, W. Meier, R. Cate, M. Sanicola, and J. V. Bonventre, "Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration," The Journal of Biological Chemistry, vol. 277, no. 42, pp. 39739–39748, 2002.
[23] T. Ichimura, J. V. Bonventre, V. Bailly et al., "Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury," The Journal of Biological Chemistry, vol. 273, no. 7, pp. 4135–4142, 1998.
[24] V. S. Vaidya, S. S. Waikar, M. A. Ferguson et al., "Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans," Clinical and Translational Science, vol. 1, no. 3, pp. 200–208, 2008.
[25] M. M. van Timmeren, M. C. van den Heuvel, V. Bailly, S. J. L. Bakker, H. van Goor, and C. A. Stegeman, "Tubular kidney injury molecule-1 (KIM-1) in human renal disease," The Journal of Pathology, vol. 212, no. 2, pp. 209–217, 2007.
[26] T. Ichimura, C. C. Hung, S. A. Yang, J. L. Stevens, and J. V. Bonventre, "Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury," American Journal of Physiology—Renal Physiology, vol. 286, no. 3, pp. F552–F563, 2004.
[27] A. B. Kramer, M. M. van Timmeren, T. A. Schuurs et al., "Reduction of proteinuria in adriamycin-induced nephropathy is associated with reduction of renal kidney injury molecule (Kim-1) over time," The American Journal of Physiology—Renal Physiology, vol. 296, no. 5, pp. F1136–F1145, 2009.
[28] W. S. Oetting, T. B. Rogers, T. P. Krick, A. J. Matas, and H. N. Ibrahim, "Urinary β2-microglobulin is associated with acute renal allograft rejection," American Journal of Kidney Diseases, vol. 47, no. 5, pp. 898–904, 2006.
[29] V. S. Klimenko, V. N. Titov, V. P. Masenko, and P. M. Leshchinski, "Beta 2-microglobulin concentration in the blood and urine," Laboratornoe Delo, no. 2, pp. 107–110, 1982.