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Impact of KIM-1 expression on the advancement of renal failure- A systematic review

[1]Swathi Silarapu , [2]Ethakota Jahnavi

ABSTRACT--*One of the major challenges that are being faced by the public healthcare is the renal failure. The suggested ancient clinical biomarkers for this renal failure are the blood urea nitrogen and serum creatinine. But now-a-days these are not considered that sensitive or specific enough as they solely increase significantly after the presence of extensive failure. Therefore there is a need to investigate more of sensitive and specific biomarkers for any type of renal failure is an important factor in nephropathies. Thus specific biomarkers that can help in detecting the injury at the disease starting stage and early diagnosis of these renal diseases would enable better and enhanced therapeutic treatment for the benefit of the individuals in terms of economic and wellbeing. Application of the recent and advanced technologies such as functional genomics, proteomics, and bio fluid profiling has revealed several new molecules that are emerging as predictive biomarkers of renal failure. The most promising and encouraging in current scenario among those include the urinary proteins such as NGAL, KIM-1, and L-FABP (liver-type fatty acid binding protein). Thus keeping all these points in view of the insensitivity and lack of specificity of the traditional and so called gold standard biomarkers the present review focuses on emphasizing the current insights of the novel biomarkers specifically (KIM-1) Kidney Injury Molecule-1. Thus this review gives an insight of the KIM-1 and its expanding evidence as biomarker for early detector in kidney damage and other kidney diseases. It also discusses about the structure, function, detection and signaling pathway.*

Keywords--*Renal failure, Kidney injury molecule, serum creatinine.*

I. INTRODUCTION

Research in the human physiology has achieved enhanced knowledge and understanding of diseases. Today treatment of diseases is able to save more lives than older days, however several areas in human physiology is still a mystery and needs more research. One of these areas is the renal diseases, which is a major health problem all over the world. The first sign for the kidney failure till now is the reduction of the kidney function and it is seen when the protein urea is measured >0.2 and the individuals are reaching to nearly stage III of the disease (Fig 1). Until now the kidney failure is being identified by the use of blood urea and serum creatinine, but these are not specific and sensitive and lack high predictive value that is proved in a research conducted by the Steubl et al. (1). He recommended that there is a rising and falling relationship between serum creatinine and estimated glomerular filtration rate (eGFR) and the

[1]*Gitam institute of technology, Visakhapatnam, rushikonda.*
[2]*Siddhartha medical college, Vijayawada.*

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creatinine concentrations were raised in the blood serum only when the kidneys were damaged to approximately 40–50%. Thus there is a lack of detection of the kidney problems at an early stage.

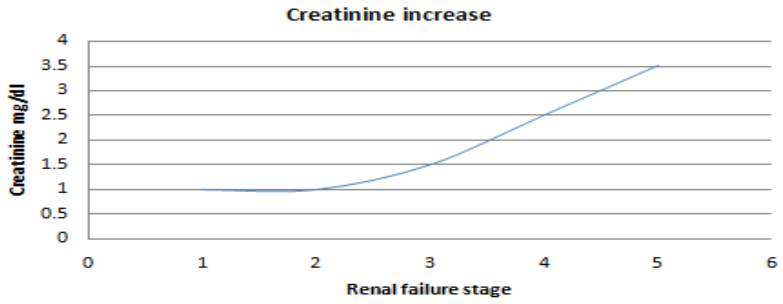

Figure 1: Graph representing the significant increase of the creatinine in the blood after the individual reached to stage III.

For this reason there is a need to identify precise and effective biomarkers that are rapid, reliable, can detect kidney disease at an early stage, site specific to detect injuries, applicable for different age groups and races. Research is being conducted on many new molecules for analyzing the potential role in early detection of the renal failure. Some of the proteins based on previous research that have been recognized as the promising biomarkers for the animal and early human studies are NGAl, IL-18, KIM-1, L-FABP, cystatin C, Tissue inhibitor of metalloproteinase-2 (TIMP-2) and Insulin like growth factor binding protein 7 (IGFBP7). (2).

II. KIDNEY INJURY MOLECULE-1

The present review article is being focused on the Kidney Injury Molecule. It is one such biomarker that is proved to be an outstanding biomarker that is being identified as an early biomarker for the kidney injuries. KIM-1 (T-cell immunoglobulin; mucin-containing molecule) is a type 1 trans-membrane protein. The structure of this molecule as shown in figure 2 consists of two portions one is the extracellular portion and the other is the cytoplasmic portion. The cytoplasmic portion is seen at very low levels in the normal levels whereas the extracellular portion that weighs about 90 KDa is seen in the blood circulation only after an ischemic damage to the kidney (3, 4). The intracellular domain is about 14 KDa called KIM-1b that contains a signaling motif for the tyrosine phosphorylation present in the renal form of protein and the extracellular ectodomain contains a six-cysteine immunoglobulin like domain. There is a high homology between the KIM-1 genes and the hepatitis A virus cell receptor that could promote the entry of virus in certain conditions (5). Thus the whole structure of the KIM-1 reiterates a conclusion of its adhesion property (6).

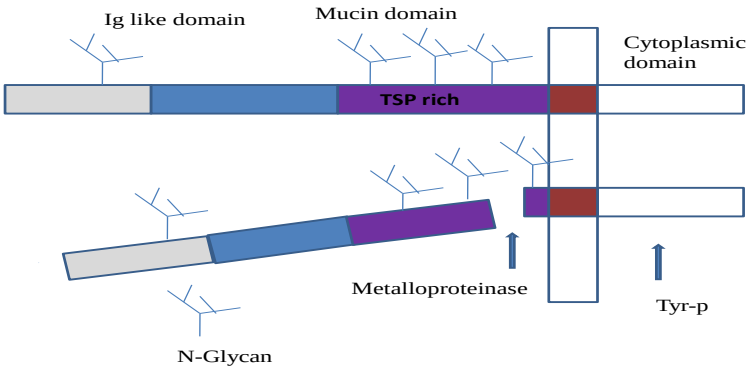

Figure 2: tyr-p

In a research done on rats by the Han et al. it is identified that KIM-1 is seen at lower levels or is absent in the disease free kidneys but is markedly visible by the proximal epithelial and proximal tubular cells after damage to the kidneys by ischemic to toxic injury (7). This molecule is also seen in higher levels in the patients affected with renal cell carcinoma that is associated with the proximal tubule cell dedifferentiation (7, 8). The shedding of this Kim-1 after the injury is regulated in part by the MAP kinase signaling pathway due to the stress that resulted in the release of a soluble kidney injury molecule (sKIM-1). In the mutagenesis studies it is shown that the juxtamembrane protein secondary structure affected susceptibility to the metalloproteinase-mediated KIM-1 cleavage (4).

The gene is up-regulated in the kidney in renal diseases, which was confirmed at the protein level (9). Right from its identification it has been identified as a sensitive and specific marker in both humans and animal models. This was confirmed in a study that within 48 hrs KIM-1 mRNA was increased in post-ischemic rats compared to any other mRNA in the analysis. This visible elevation of this molecule was also confirmed in other studies (10). Amin RP et. al. have shown that urinary KIM-1 was established to be good marker for detectable changes in eGFR on rats on mice. (11). Compared to serum creatinine the tissue and urinary KIM-1 is proved to be a faster and superior maker in a Cisplastin-induced nephrotoxicity (4). KIM-1 is known to be a potential biomarker for chronic disease mediated by the tubular interstitial damage (12).

Recent advancements in the molecular biology helped to detect discover robust methods to detect the KIM-1. In that one is the micro bead based KIM-1 ELISA to facilitate the urinary KIM-1 as a biomarker for acute kidney injury in animal models (13) and the other is the laminar flow dipstick assay (14). Using these methods one can measure KIM-1 levels in the urine and serum in a rapid manner. In some studies they also demonstrated the correlation between the progression of the KIM-1 and the degree of renal function (15). It was demonstrated that urinary KIM-1 is in higher levels in patients with chronic kidney disease than in acute kidney injury that was proved in a research done of three rat models that KIM-1 levels are increased at an early stage and persistently increased in renal fibroids and may play a pivotal role in macrophage activation via the MAPK pathway in kidney disease (16). Thus KIM-1 is not only recognized as an early biomarker for the acute kidney injury but also has a budding role in the prediction of long term renal failure.

By the Support of the research results, significance and the impact on the upregulation of the chronic kidney diseases, the US Food and Drug Administration and the European Medicines Agency noticed KIM-1 as urinary biomarker in the perspective of drug-induced nephrotoxicity in rat models (17).

In several studies it has been demonstrated that KIM-1 can differentiate patients with different types of tubular necrosis. It can differentiate patients from acute graft rejection and ill patients from those without Acute Kidney Injury (18).

In a study it is identified that urine samples were stable for the detection of KIM-1 for 48hrs if stored at 4℃and for 6 months if stored at a temperature of -80℃ (19). The concentrations of the urinary KIM-1 were also related to the pre-freezing and thawing time. If the samples were frozen and thawed several times then it will adversely affect the KIM-1 measurement. Hence it is suggested that the urine samples should freeze within 3h after the collection and should thaw or defreeze before the measurement (19).

KIM-1 has a dual role in acting as a biomarker and also in repair of the proximal tubule repair. In a study it is indicated that the transition from normal to dedifferentiation cells is associated with an upregulation of the KIM-1 expression but the mechanism is not yet clear (6).

Significant positive linear progression is obtained in correlation between the KIM-1, age and sex (21) but in recent study it is revealed that there is no association between the KIM-1 elevation and sex (22).

III. CONCLUSION

KIM-1 is expressed in the proximal tubule epithelial cells and is absent or expressed in low amounts in the normal kidneys. But in the diseased state to the kidneys it is up-regulated as the extracellular portion will be cleaved after an injury. Thus it is recommended as sensitive biomarker for the renal proximal tubule damage. It also plays an important role in regeneration process of the tubule epithelial cells. In the case of cancers associated with the kidney the increased levels of urinary KIM-1 expression is an indication for the renal tumor pathological process. Thus it is a sensitive, specific and early biomarker of kidney injury in acute and chronic condition. Thus it can be used to predict the progress and outcome of kidney disease.

REFERENCES

1. Steubl D, Block M, Herbst V, Nockher WA, et al. Plasma uromodulin correlates with kidney function and identifies early stages in chronic kidney disease patients. Medicine 2016; 95: 3011.
2. Parikh CR, Thiessen-Philbrook H, Garg AX, et al. TRIBE-AKI Consortium Performance of kidney injury molecule-1 and liver fatty acid-binding protein and combined biomarkers of AKI after cardiac surgery. Clin J Am Soc Nephrol 2013; 8: 1079–1088.
3. De Silva PMCS, Mohammed Abdul KS, Eakanayake EM, et al. Urinary biomarkers KIM-1 and NGAL for detection of chronic kidney disease of uncertain etiology (CKDu) among agricultural communities in Sri Lanka. PLoS Negl Trop Dis 2016; 10: 4979.
4. V Bailly Z, Zhang W, Meier R, Cate M, et al, Shedding of kidney injury molecule-1, a putative adhesion protein involved in renal regeneration. The Journal of Biological Chemistry 2002; 277(42): 39739–39748.
5. Kaplan G, Totsuka A, Thompson P, et al. Identification of a surface glycoprotein on African green monkey kidney cells as a receptor for hepatitis A virus. EMBO J 1996;15: 4282–4296.

6. Ichimura T, Bonventre JV, Bailly V, et al., Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesionmolecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. Journal of Biological Chemistry 1998; 273(7): 4135–4142.
7. Han WK, Alinani A, Wu CL, et al. Human kidney injury molecule-1 is a tissue and urinary tumor marker of renal cell carcinoma. J Am Soc Nephrol. 2005 Apr;16(4):1126-34
8. van Timmeren MM, van den Heuvel M C, Bailly V, et al. Tubular kidney injury molecule-1 (KIM-1) in human renal disease. The Journal of Pathology 2007; 212(2): 209–217.
9. Chimura T, Hung CC, Yang SA, Stevens JL, et al. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol 2004; 286: 552–563.
10. Amin RP, Vickers AE, Sistare F, et al. Identification of putative gene based markers of renal toxicity. Environ Health Perspect 2004; 112: 465–79.
11. Zeisberg M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. J. Am. Soc. Nephrol 2010; 21: 1819–1834.
12. Slocum J L, Heung M, Pennathur S. Marking renalinjury: can we move beyond serum creatinine?. Translational Research 2012; 159(4): 277–289.
13. Sabbisetti VS, Ito K, Wang C., et al. Novel assays for detection of urinary KIM-1 in mouse models of kidney injury. Toxicological Sciences 2013; 131(1): 13–25.
14. Kramer AB, van Timmeren MM, Schuurs TA, et al. Reduction of proteinuria in adriamycin-induced nephropathy is associated with reduction of renal kidney injury molecule(Kim-1) over time, American Journal of Physiology—RenalPhysiology 2009; 296(5):1136–1145.
15. Shao X, Xie Y, Wang Q, et al. · Mou S. Kidney Injury Molecule-1 is Elevated in Nephropathy and Mediates Macrophage Activation via the Mapk Signalling Pathway Tian L. · Cell Physiol Biochem. 2017;41(2):769-783
16. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann. Intern. Med 2008; 148: 810–819.
17. van de Vrie M, Deegens JK, van der Vlag J, et al. Effect of long-term storage of urine samples on measurement of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Am J Kidney Dis 2014; 63: 573–576
18. U.S. Food and Drug Administration: FDA, European Medicines Agency to consider additional test results when assessing new drug safety: Collaborative effort by FDA and EMEA expected to yield additional safety data.
19. van de Vrie M, Deegens JK, van der Vlag J, et al.. Effect of long-term storage of urine samples on measurement of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL). Am J Kidney Dis. 2014; 63: 573–576.
20. Pennemans V, Rigo JM, Penders J, et al. Collection and storage requirements for urinary kidney injury molecule-1 (KIM-1) measurements in humans. Clin Chem Lab Med. 2012; 50: 539–543.
21. Pennemans V, Rigo JM, Faes C, et al. Establishment of reference values for novel urinary biomarkers for renal damage in the healthy population: Are age and gender an issue?. Clin Chem Lab Med 2013; 51:1795–1802.
22. McWilliam SJ, Antoine DJ, Sabbisetti V, et al. Reference intervals for urinary renal injury biomarkers KIM-1 and NGAL in healthy children. Biomark Med. 2014; 8: 1189–1197.

23. Alam, M. SHABBIR, et al. "Effect of khat (Catha edulis) consumption on the functions of liver, kidney and lipid profile in male population of Jazan Region of Kingdom of Saudi Arabia." Inter J Applied Natural Sci 3.2 (2014): 9-14.
24. ARQUEZ, HUMBERTO FERREIRA. "BILATERAL VARIATIONS IN THE BLOOD SUPPLY OF KIDNEYS." International Journal of Research in Applied, Natural and Social Sciences (IMPACT: IJRANSS) 2.4 (2014):79-84
25. Sharma, Surinder K., Indira R. Samal, and SOUMYA NP. "Urinary Stones in Southern India: Biochemical Analysis and its Clinical Implications." International Journal of General Medicine and Pharmacy (IJGMP) 4.1 (2015): 93-100.
26. SIREESHA, D. MANASA, N. SRIVIDYA, and KVSB VIDYA SAGAR. "A STUDY ON AEROBIC BACTERIAL ISOLATES FROM PATIENTS SUFFERING FROM SYMPTOMATIC URINARY TRACT INFECTION." International Journal of General Medicine and Pharmacy (IJGMP) 6.4 (2017):1-6
27. Agyeman-Yeboah, J. O. A. N. A., and KWADWO AMEYAW Korsah. "Determinants of clinical utilizations of the nursing process by nurses: a study at the 37 Military Hospital, Accra." International Journal of General Medicine and Pharmacy (IJGMP) 5.6 (2016): 1-23.
28. Abed, ALAA HUSSEIN. "Violence against emergency care staff in Basra hospitals." International journal of medicine and pharmaceutical sciences (IJMPS) 4.2 (2014): 99-110.