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Research Article

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KIM-1 as a biomarker to predict and diagnose Acute Kidney Injury (AKI)

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ABSTRACT

Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane protein, is expressed in dedifferentiated proximal renal tubular epithelial cells in damaged regions. It may participate in the progress of renal injury or repair. Many studies have illustrated the different functions of KIM-1 in various renal diseases including protective functions in acute kidney injury and damaging functions in chronic kidney Disease. Studies have also shown the importance of this protein in prediction and diagnosis of acute renal injury as it starts to elevate after 6-12 hours of injury occurrence compared with creatinine which needs 2-3 days to rise. Urine and Serum levels of KIM-1, creatinine, urea and uric acid were measured in samples gathered from 85 patients divided into 4 groups as following:
- Patients with acute renal injury (ARI).
- Patients with chronic renal injury (CRI).
- Patients who had acute renal attack after they had been diagnosed with chronic kidney injury.
- High risk individuals from whom samples were collected 2 hours and 3 days after the occurrence of the acute injury.
We found higher levels of KIM-1 in patient groups as compared to control group. We also found higher levels of KIM-1 in High risk individuals as compared to controls while the levels of creatinine and urea were still within the normal range. However, the three parameters were increased in samples taken after three days of injury. We found that urine and serum levels of KIM-1are elevated earlier in acute renal injury. Thus KIM-1 level can be used as a predictor of acute renal injury.

Key words: KIM-1, acute renal injury, chronic renal injury.

INTRODUCTION

Acute kidney injury (AKI) refers to a common syndrome that results from multiple causative factors and occurs in a variety of clinical settings, with varied clinical manifestations, ranging from a minimal elevation in serum creatinine to anuric renal failure. AKI is characterized functionally by a rapid decline in the glomerular filtration rate (GFR), and biochemically by the resultant accumulation of nitrogenous wastes such as blood-urea nitrogen and creatinine.

The term AKI has largely replaced acute renal failure, since the latter designation overemphasizes the failure of kidney function and fails to account for the diverse molecular, biochemical and structural processes that characterize the AKI syndrome.[1] Renal failure causes deficiency in the production of waste containing nitrogen, which is usually measured by urea causing an elevation in the concentration of urea in the serum or the so-called Uraemia.
Uraemia classified into:
- Prerenal.
- Renal.
- Postrenal.[2]

In recent years, several biomarkers were developed to investigate acute renal failure quickly and specifically, one of which is the Kidney Injury Molecule (KIM-1). Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane tubular protein, is undetectable in normal kidneys, but it is markedly induced in renal injury including acute kidney injury (AKI) and chronic kidney disease (CKD).[3-4-5]

Many studies indicate that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis.[6-7]

It's a transmembrane glycoprotein containing in its extracellular portion a 6-cysteine immunoglobulin-like domain and a Thr/Ser-Pro rich domain characteristic of mucin like O-glycosylated proteins. Immunoglobulin-like domains have been widely implicated in mediating protein-protein interaction in particular at the cell surface. Kidney injurymolecule-1 also has a transmembrane domain and a cytoplasmic domain, and the latter contains a conservative tyrosine phosphorylation site that can be phosphorylated by tyrosine, indicating that KIM-1 may be a signaling molecule.[8]

KIM-1 was expressed in dedifferentiated and regenerative proximal tubular epithelial cells in damaged regions after toxic or ischemic injury, Therefore, KIM-1 may play a role in the regeneration process of tubular epithelial cells, through which it can help reconstitute a continuous epithelial layer.[3-4-9]

In renal patients, KIM-1 is elevated in a variety of conditions including ischemia, nephrotoxic drugs, CKD, and acute/chronic renal transplant dysfunction. There are an increasing of studies that demonstrate the use of KIM-1 as a marker for kidney injury including acute and chronic kidney injuries. KIM-1 is not expressed in normal kidney but specifically expressed in injured proximal tubular cells, and such an expression can persist until the damaged cells have completely recovered. Thus it can be an ideal biomarker of kidney injury. Moreover, the rapid and integrated cleavage of its ectodomain into the lumens of kidney tubules can make it detectable in urine.[10] Quantitation of urinary KIM-1 is likely to be a noninvasive and sensitive method for the evaluation of kidney injury and even for monitoring the therapeutic effects of kidney injury because urinary KIM-1 level is closely related to tissue KIM-1 and correlates with the severity of renal damage.[11] In the study of nephrotoxicity, urinary KIM-1 levels increased severely earlier than the increases of blood urea nitrogen and plasma creatinine.[12]

In addition, recent findings by Ichimura et al demonstrated that KIM-1 was a phosphatidylserine receptor that conferred on epithelial cells the properties of highly phagocytic cells.[13]

EXPERIMENTAL SECTION:

Study groups

Our study included 65 individuals from whom urine samples were collected and they were divided into the following groups: patients with acute renal injury (ARI) (18 patients). patients with chronic renal injury (CRI) (4 patients). patients who had acute renal attack after they had been diagnosed with chronic kidney injury (7 patients).

High risk individuals from whom samples were collected 2 hours and 3 days after the occurrence of the acute injury (20 patients). 16 healthy individuals as a control group. Informed consent was taken from all recruited individuals in this study.

Materials and methods

The following parameters were assayed in all studied individuals: KIM-1: was assayed using Human KIM-1 ELISA kit manufactured by SunRed company, China. Creatinine: using kit manufactured by Spinreact company, Spain. Urea: using kit manufactured by Spinreact company, Spain.

Statistics

Statistical study was performed using Prism GraphPad version 5 and Microsoft Excel 2010. Values were expressed by mean ± standard deviation. We used pearson correlation coefficient to study the correlation between variants of the same group. T-test was used to compare between different study groups. A P-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

KIM-1 levels were assayed in urine samples from both the control group and acute kidney injury(AKI) patients. A significant elevation was found in urinary KIM-1 values in AKI patients as compared to controls ($P<0.0001$). Thus, indicating an elevation in KIM-1 levels in acute kidney injury. This can be explained by the excessive damage to

renal tubular epithelial cells caused by different kidney injury stimulating factors which results in elevated urinary KIM-1 concentrations.

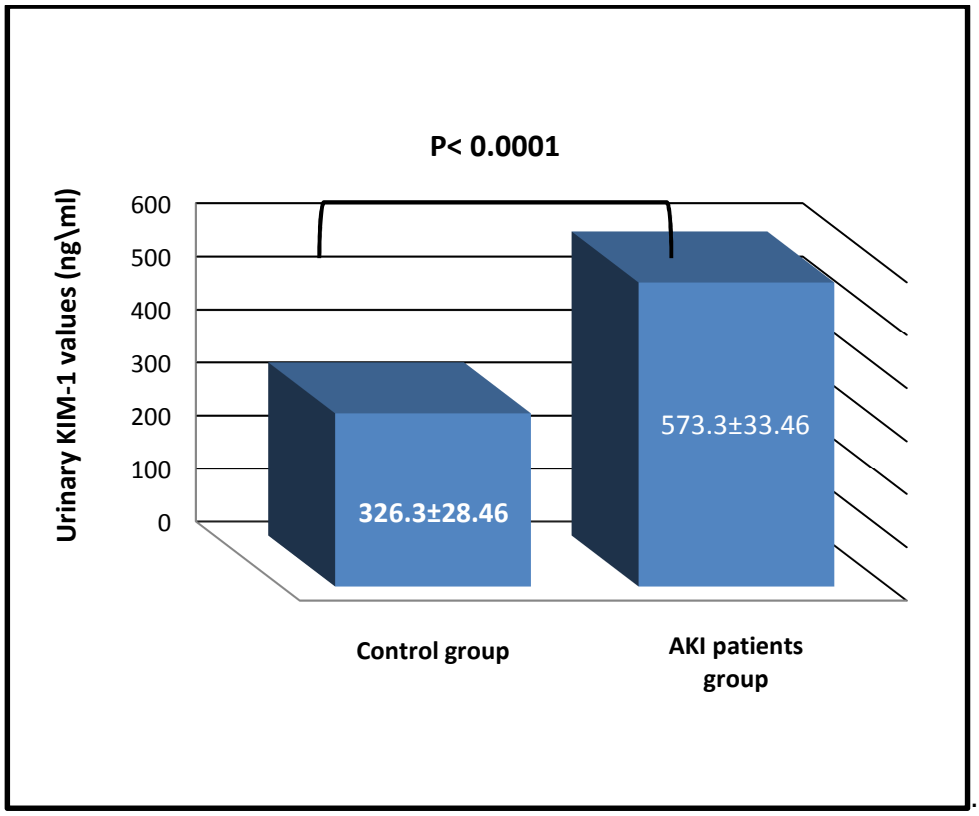

Figure 1: urinary KIM-1 values in control group and AKI patients group

When urinary KIM-1 values were determined in control group and high risk individuals group, significantly higher KIM-1 values were found in high risk individuals as compared to controls (P<0.0001). Thus, indicating an increased KIM-1 levels in acute injuries. KIM-1 may be useful in early detection of acute kidney injury as its levels begin to increase earlier than traditional markers of kidney injury (urea and creatinine).

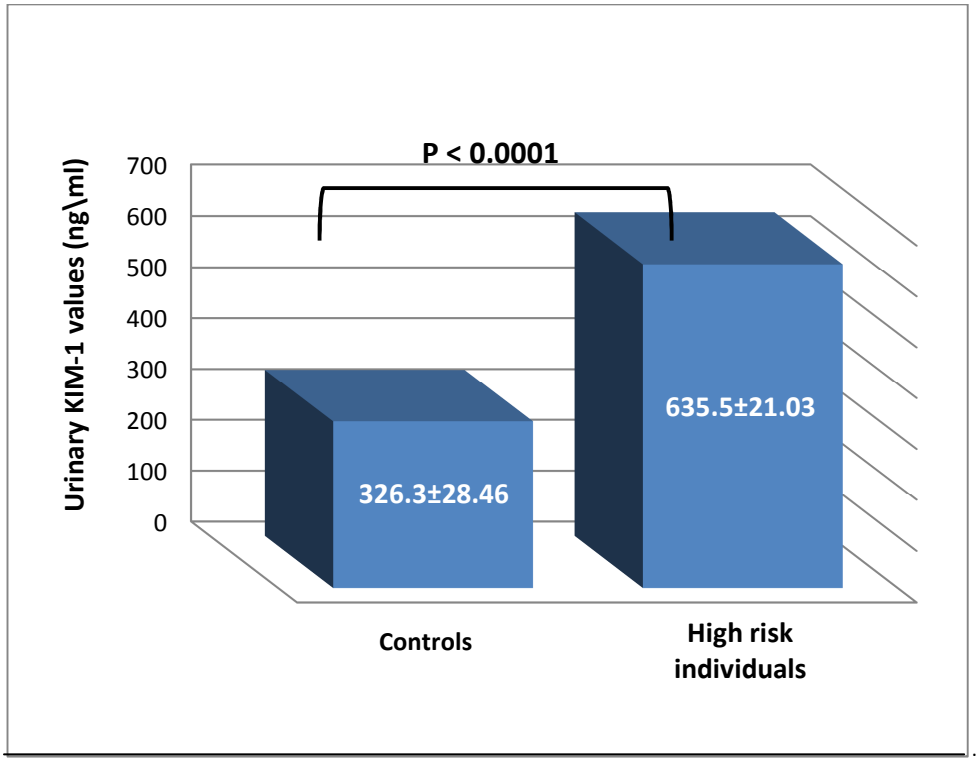

Figure 2: urinary KIM-1 values in control group and High risk individuals group

Urinary KIM-1 levels were measured in both the control group and chronic kidney diseases (CKD) patients. A significant elevation was found in urinary KIM-1 values in CKD patients as compared to controls (P=0.0001).

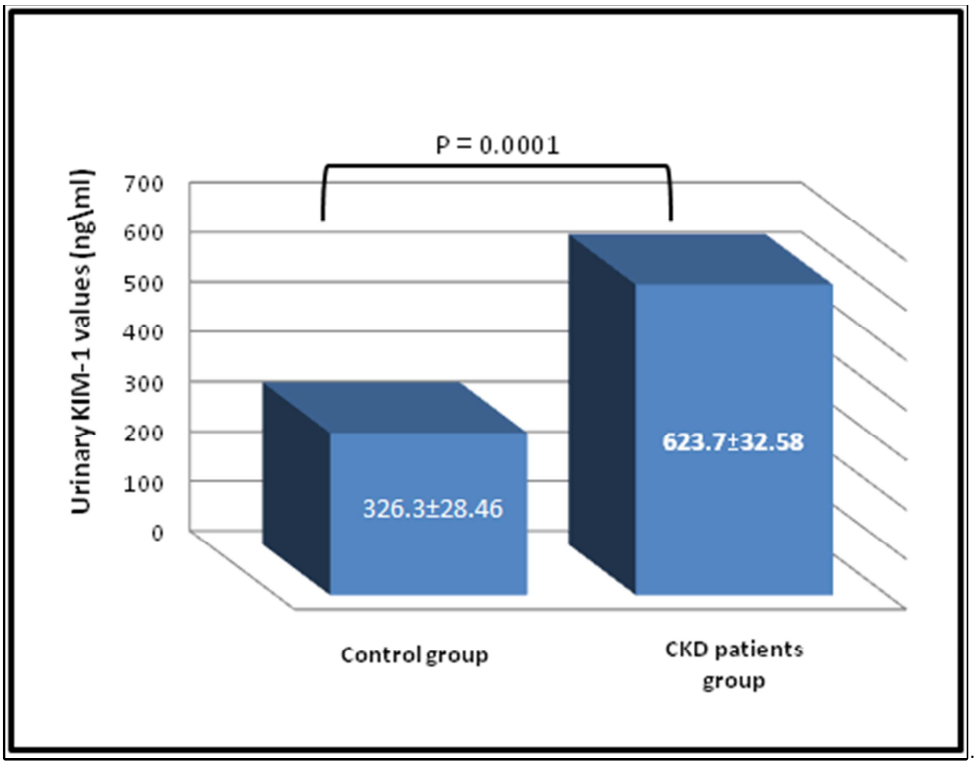

Figure 3: urinary KIM-1 values in control group and CKD patients group

Urinary KIM-1 was assayed in the control group and in a group of patients who had acute renal attack after they had been diagnosed with chronic kidney injury. A significant elevation was found in urinary KIM-1 values in the

patients group as compared to the controls (P<0.0001). The progressive renal damage accompanying acute kidney injury on a chronic background is associated with increasing KIM-1 gene expression levels.

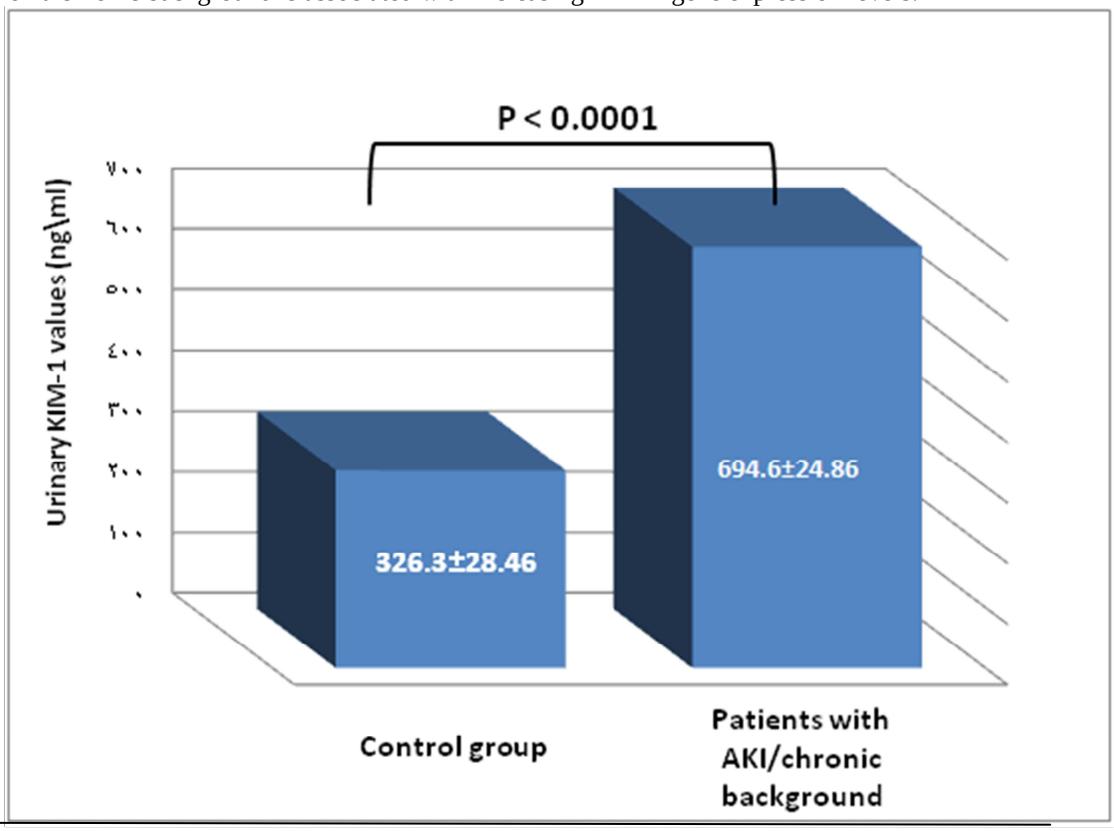

Figure 4: KIM-1 values in control group and AKI/CKD patients group

Our study showed a significant positive correlation (r=0.88) between serum and urinary levels of KIM-1 in AKI and AKI/CKD patients group.

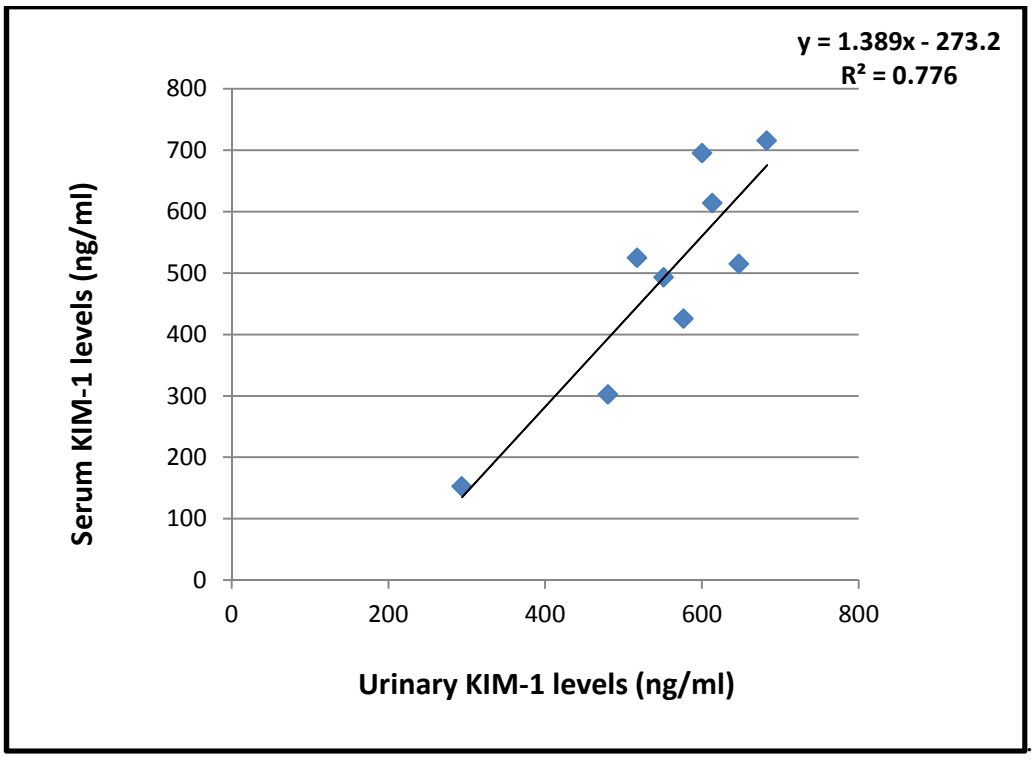

Figure 5: correlation between serum and urinary levels of KIM-1 in AKI and AKI/CKD patients group

Our study showed a significant elevation in urinary KIM-1 concentrations in all studied patient groups compared to the control group. The highest values were found in acute kidney injury patients. Thus, KIM-1 may be considered as a an important marker of acute kidney injury. The progressive damage in renal tubular cells accompanying acute and chronic kidney injuries which increases when CKD patients have an acute attack leads to an excessive secretion of KIM-1 and as a result both serum and urinary levels of this protein are increased. our study also showed that KIM-1 levels had increased early after the incidence of acute injury while both creatinine and urea levels were still normal. KIM-1 may be a predictor of acute kidney injury that makes it possible to prevent the incidence of permanent irreversible kidney damage.

The results agreed with the results of Bonventre his colleagues in 2009[11] and Prozialeck study and his colleagues in 2009.[12]

Our study showed a significant positive correlation between serum and urinary levels of KIM-1 in AKI and AKI/CKD patients group that lead to Urinary KIM-1 level is closely related to tissue KIM-1 The results agreed with the results of Simic his colleagues in 2011.[14]

CONCLUSION

KIM-1 may be useful in the prediction and early diagnosis of acute kidney injuries as its levels begin to increase earlier than urea and creatinine and it can be a prognostic factor that prevents the progression of complications.

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http://damasuniv.edu.sy/english

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