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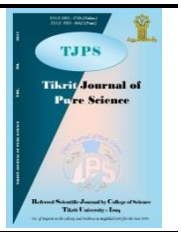

The Relation between Kidney Injury Molecule -1 and its role as promising biomarker in kidney stone patients

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Abstract

Urea and creatinine is the most sensitive markers of Kidney Diseases progression in clinical practice, especially when combined with GFR, but these have limitations. Hence, early, more sensitive, biomarkers are required. Recently, promising biomarkers have been identified for CKD progression such as kim-1 has been investigated as a novel biomarkers of kidney diseases progression. This study aimed to evaluate urinary Kidney Injury Molecule-1(KIM-1) in kidney stone patients.75 patients diagnosed with renal stone diseases and all patients were screened and followed up in the out-patients clinics in Salah Adin general hospital. controls were represented by 15 healthy volunteers. KIM-1, levels shows no significant changes within patients groups while shows that the KIM-1 levels were significantly increased in stone patients when compared with the healthy controls ($P<0.05$). Total protein and S. Albumin levels significantly decreased in patients group compared to the controls levels while there was no significant changes within patients group. The current results suggest that KIM-1 can consider as promising biomarker for diagnosis, clinical progression and investigations for kidney stone diseases.

Introduction

Kidney stones is a problem affecting 1–20% of population worldwide [1]. There are many types of renal stones, the most abundant are found by chemical analysis calcium oxalate (CaOx) [2]. The pathogenic mechanisms of stone formation remain unclear. One of the hypothesis is that stone formation is a result of multistep process, crystal nucleation, growth, and aggregation [3]. Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein expressed on renal proximal tubule epithelial cells undergoing regeneration after toxic or ischemic injury. The extracellular domain of KIM-1 is composed of an immunoglobulin-link domain that points to a possible role in cell adhesion by homology to several known adhesion proteins [4]. Many studies indicate that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of diagnosis [5]. Several recent studies have suggested the usefulness of Kidney Injury Molecule -1 (KIM-1) as an early indicator for renal injury resulting from chemical toxicity or ischemic injury [6,7]. KIM-1 was first identified as a putative cell adhesion molecule that can recognize and induce phagocytosis of dead cells in the tubular lumen of the kidney [8]. Expression of KIM-1 is up-regulated during tubular injury, but most importantly, the stable codomain is cleaved from the membrane anchor and can be detected in the urine. This phenomenon has been observed in rodent and human models of nephrotoxicity including in Renal Cell Carcinoma [9]. KIM-1 has been suggested to be an ideal biomarker in many chemical and pathological nephrotoxicity models due to its robust and marked expression in the injured state.[10].

Kidney injury molecule 1 (KIM-1) has been investigated as a sensitive marker of acute ischemic injury of the proximal tubular cells.[11] KIM-1 is excreted in urine and thus has been used as a biomarker for acute kidney injury mostly in the renal transplant population.[12] . The aim of the study is to investigate the role of KIM-1 as a biomarker in kidney stone patient.

Patients and Methods

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A cross section study done in Tikrit city for the period from September 2017 to January 2018. The current study included 75 patients with kidney stone diseases 49 were males and 26 were females there ages range was 35-50 years. All patients were screened and followed up in out-patients clinics in Salah-Aden general hospital. Also,15 healthy volunteers (5femals and 10 males) served as controls.
A blood and first morning urine sample was obtained from all patients and healthy volunteers.
Blood and urine was centrifuged at 3000 RPM for 10 min at 4°C. Aliquots were transferred into tubes, snap frozen and stored at- 20°C until further use. KIM-1 was determined in the urine by using enzyme-linked immunosorbent assay (ELISA) kits (KIM-1 Elabscience- USA) according to the manufacturer's instructions.

Statistical Analysis:

Statistical analysis the results was performed using Statistical Package for the Social Sciences software (SPSS), for windows 7.All data were presented as mean ±S.D (standard deviation). ANOVA test were used to compare between means of variables between males and females and within the same gender group, *p* values less than 0.05 were used as significant value.

Result and discussion

Figure 1 and Figure 2 , shows no significant changes within patients groups while there was a significant changes between patients and controls, the mean value of total protein and serum albumin is significantly decreased in renal calculi patients when compared to control($P < 0.05$).

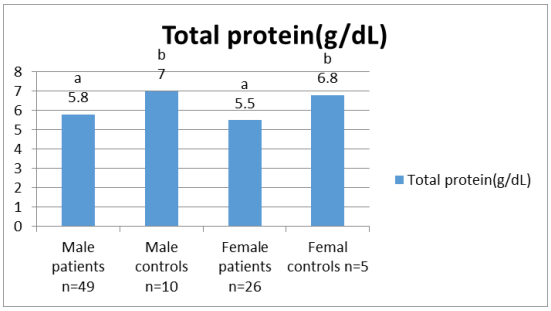

Figure 1 serum Total protein levels in Healthy Controls and renal calculi patients. (the deferent liters mean there is a significant differences at p≤0.05).

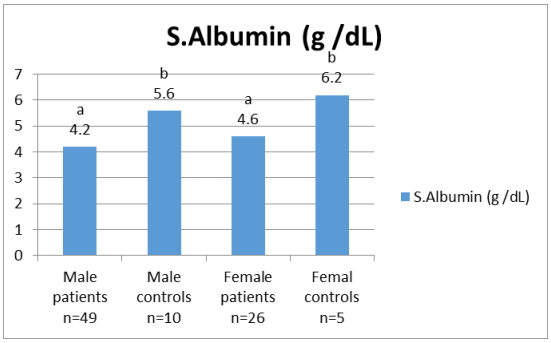

Figure 2 Serum Albumin (S. Albumin) levels in Healthy Controls and renal calculi patients. (the deferent liters mean there is a significant differences at (p≤0.05).

Total protein and serum albumin is a well-known marker of nutrition in patients. There was a linear increase in death rate with declining total protein and serum albumin levels in the dialysis patients. Many patients with kidney disease develop the nephrotic syndrome, which is characterized by loss of large quantities of plasma proteins into the urine. In some instances, this occurs without evidence of other major abnormalities of kidney function, but more often it is associated with some degree of renal failure[13]
Low levels of total protein ,lower than – normal, may be due to malnutrition[14] which is one of the most common kidney complications and /or renal failure (RF). The other reason for the decline in total protein concentration in the blood serum of these patients due to the damage happening in the renal tissues leading to kidney loss and leakage of protein in large quantities through the damaged tissues of the kidney and therefore its glomerular filtration rate decreased. Normally, proteins are too large to pass through the kidneys, however, they are able to pass through when the glomeruli are damaged. Decreased levels of serum albumin may be a sign of kidney diseases [15].
Figure 3 shows no significant changes within patients groups while shows that the KIM-1 levels were significantly increased in stone patients when compared with the healthy controls ($P < 0.05$).

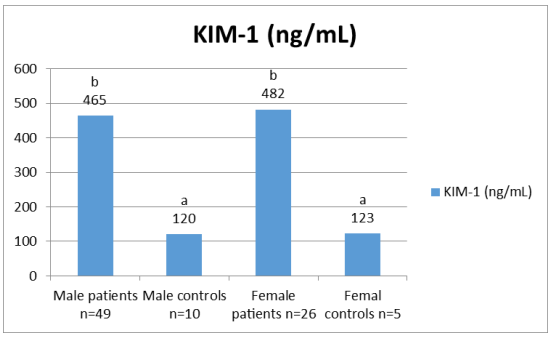

Figure 3 KIM-1 levels in Healthy Controls and renal calculi patients. (the deferent liters mean there is a significant differences at p≤0.05).

KIM-1 is a transmembrane tubular protein with uncertain function, not detectable in the normal kidney, but elevated in experimental and clinical kidney damage KIM-1 expression is significantly increased within kidney biopsy tissue collected from patients with kidney disease. It is increased in the urine in acute kidney injury (AKI) and kidney disease, [16] and increased in kidney transplant patients and associated with graft loss.[17].
Experimental studies suggest that KIM-1 may be an indicator of AKI to chronic kidney deceases (CKD) transition[18]. A retrospective study in proteinuric nondiabetic kidney disease patients found elevated levels of urinary KIM-1. In addition, urinary KIM-1 decreased with short-term antiproteinuric therapies [19]. The diagnostic performance of KIM-1 in animal models as a predictor of drug-induced kidney injury was recently evaluated alongside more traditional

serum creatinine and blood urea nitrogen and urinary N-acetyl-b-O-glucosaminidase (NAG), [20] where KIM-1 levels better correlated with the degree of kidney tubular histopathology, suggesting that KIM-1 measurement could facilitate elimination of potentially nephrotoxic drug candidates. Lower urinary levels of KIM-1 were associated with the regression of microalbuminuria in patients with type 1 diabetes mellitus [21]. An increase in urinary KIM-1, that is only fractionally expressed under physiological conditions, reflects tubular damage in the proximal S3 tubule segment as shown in acute and chronic kidney injury. KIM-1 expression was found in murine polycystic kidneys but not in wild type mice[22]. KIM-1 has also been identified as novel ciliary molecule. By interacting with the PKD2 Protein Transient Receptor Potential Polycystic 2, KIM-1 may be involved in cellular response to changes in extracellular fluid flow detected by the cilium. [23]. In a study of Meijer et al increased KIM-1 levels in 24h urine samples of autosomal dominant polycystic kidney disease (ADPKD) patients were associated with total kidney volume, adjusted for age, gender and albuminuria compared with healthy volunteers. [24].

Conclusions and Recommendations

The results reveal that KIM-1 has the ability to early identify individuals at risk, and the changes in KIM-1 might predict disease progression.

Therefore, further clinical testing and longitudinal surveys with more patients are necessary to relay on KIM-1 test in clinical use .

The ELIZA test kit that used for estimation of KIM-1 levels are relatively expensive therefore the development of a new cheaper test method is needed .

Table of Results

Table 1: KIM-1, Total protein and S.Albumin levels in healthy Controls and kidney stone patients

Biochemical Parameters	Healthy Controls (Mean ± SD) n.=15		Patients (Mean ± SD) n.=75		p. value
	Male n=10	Female n=5	Male n=49	Female n=26	
KIM-1(ng/mL)	120 ± 20	123 ±12	465 ±43	482 ±21	0.05
Total protein(g/dL)	7 ±0.6	6.8 ±0.3	5.8 ±0.3	5.5 ±0.5	0.05
S.Albumin (g /dL)	5.6 ±0.4	6.2 ±0.1	4.2 ±0.2	4.6 ±0.3	0.05

* P < 0.05 Significant

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العلاقة بين Kidney Injury Molecule -1 ودورة كمؤشر حيوي واعد في مرضى حصى الكلى

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الملخص

تعد اليوريا والكرياتنين أكثر المؤشرات حساسية لتطور أمراض الكلى في التطبيقات السريرية، وخاصة عندما تقترن مع معدل الترشيح الكبيبي، ولكن هذه المؤشرات لها حدود. ولهذا، برزت الحاجة الى مؤشرات حيوية مبكرة أكثر حساسية. في الآونة الأخيرة، تم تحديد العديد من المؤشرات الحيوية الواعدة مثل kim-1 كمؤشرات حيوية جديدة لتطور أمراض الكلى. هدفت هذه الدراسة إلى تقييم مستويات KIM-1 في مرضى حصى الكلى. تم فحص 75 مريضا تم تشخيص إصابتهم بحصى الكلى في العيادات الاستشارية بمستشفى صلاح الدين العام. تم تمثيل عينة السيطرة بـ 15 متطوعا أصحاء. اظهرت النتائج عدم وجود فروق معنوية ضمن مجموعة المرضى بينما اظهرت وجود ارتفاع معنوي في معدلات ال KIM-1 في المرضى مقارنة مع المجموعة الضابطة عند مستوى معنوية ($P \leq 0.05$). واظهرت النتائج للبروتين الكلي ومستويات البومين المصل وجود انخفض معنوي بشكل ملحوظ في مجموعة المرضى مقارنة بالسيطرة بينما لم تكن هناك فروقات ضمن مجموعة المرضى. تشير النتائج الحالية إلى أن KIM-1 يمكن اعتباره مؤشر حيوي واعد للتشخيص والتطور السريري والتحقيقات المتعلقة بأمراض الكلى.