CASE REPORT INTERNATIONAL JOURNAL OF PURE MEDICAL RESEARCH

Medicine

KEYWORDS: Rotavirus, Pediatric diarrhoea, clinical pattern, seasonal effect

VALUE OF URINARY KIDNEY INJURY MOLECULE-1 LEVEL AS A MARKER OF NEPHROPATHY IN HYPERTENSIVE PATIENTS

Volume-4, Issue-5, May - 2019 ISSN (O): 2618-0774 | ISSN (P): 2618-0766

Mahmoud Hassan S Khedr* Internal Medicine Dep. Faculty of Medicine, Minia University, Egypt. *Corresponding Author mahmoud.znaty@yahoo.com

Eglal M.S Hamed Internal Medicine Dep. Faculty of Medicine, Minia University, Egypt.

Safaa M. H. Ali Internal Medicine Dep. Faculty of Medicine, Minia University, Egypt.

Hend M.Moness Clinical Pathology Dep. Faculty of Medicine, Minia University, Egypt.

Eman S. Mohamed Community Medicine Dep. Faculty of Medicine, Minia University, Egypt.

Article History
Received: 18.02.2019
Accepted: 03.04.2019
Published: 10.05.2019

ABSTRACT

Kidney injury molecule-1(KIM-1) is a type I membrane protein, comprising an extracellular portion and a cytoplasmic portion which is expressed at very low level in normal kidney. The extracellular portion can cleave and rapidly enter tubule lumens after kidney injury and can be detected in urine[8]. Plasma KIM-1 level also can specifically reflects acute and chronic kidney injury[9]. Tissue KIM-1 expression is one of the best predictor of kidney function[10]. Urinary KIM-1 levels reflect tissue KIM-1 and is associated with inflammation and renal function loss[11]. It has been shown to be a good predictor of renal injury prior to detectable changes in eGFR[12]. Thus, it can be used as a sensitive, noninvasive, and quantitative biomarker for diagnosis and monitoring of kidney injury.

Introduction:

Hypertension (HTN) affects more than 40% of adults older than the age of 25 years, it is a leading global risk factor for death or disability(1) Number of adults with HTN has increased from 594 million in 1975 to 1.13 billion in 2015(2). HTN is a common health problem in Egypt with an overall prevalence rate of 17.6% reported by the Egypt Demographic and Health Survey 2008(3). Its incidence increases with age, around 50% of Egyptians over the age of 60 years have HTN(4). Its rates of awareness, treatment and control are low. Management of HTN in Egypt is not easy because of treatment . cost is a common cause of interruption of therapy(5)

HTN is one of the most common complication and cause of chronic kidney disease (CKD) and end stage renal disease. Hypertensive nephropathy is the second most common cause of ESRD in Egypt(6). It is responsible for 29.7% of cases of ESRD in Cairo, 28.9% in Lower Egypt governorates, 25% in Upper Egypt governorates, 27.3% in Suez Canal governorates(7).

The earliest and least invasive indicator known of hypertensive nephropathy is the presence of micro albuminuria (MAU) and glomerular filtration rate (GFR) measurement. However, MAU is not specific to kidney diseases only. Therefore, there is a need for a marker that identifies hypertensive nephropathy at its early stages.

Kidney injury molecule-1(KIM-1) is a type I membrane protein, comprising an extracellular portion and a cytoplasmic portion which is expressed at very low level in normal kidney. The extracellular portion can cleave and rapidly enter tubule lumens after kidney injury and can be detected in urine(8). Plasma KIM-1 level also can specifically reflects acute and chronic kidney injury(9). Tissue KIM-1 expression is one of the best predictor of kidney function(10). Urinary KIM-1 levels reflect tissue KIM-1 and is associated with inflammation and renal function loss(11). It has been shown to be a good predictor of renal injury prior to detectable changes in eGFR(12). Thus, it can be used as a sensitive, noninvasive, and quantitative biomarker for diagnosis and monitoring of kidney injury.

Aim of the work : To detect level of urinary KIM-1 in hypertensive patients and in normal healthy controls, also to study its association with micro albuminuria and GFR and to study its predictive value in early diagnosis of CKD.

Patients and Methods:

Our present case control study was conducted on 120 persons from our hypertension out-patient's clinic, Minia University Hospital from the period of November 2016 till April 2017. The study included 80 patients already diagnosed as having Essential hypertension and were classified into two groups according to their duration of hypertension: Group A: Included 40 patients with a disease duration less than 5 years, they were 14 (35%) males and 26 (65%) females. Their age ranged from 35-50 years (mean age was 45.6±4.8). Group B: Included 40 patients with a disease duration more than 5 years, they were 15 (37.5 %) males and 25 (62.5%) females. Their age ranged from 35-50 years (mean age was 46.8±3.8).. Group C:Included 40 healthy volunteer, age, sex and BMI matched with the patient groups as a control group, they were 21 (52.5%) males and 19 (47.5%) females. Their age ranged from 35-50 years (mean age was 45.2±3.5).

The study was approved by the hospital's research ethics board. All patients provided written informed consent.

Inclusion criteria: Age: from 35 to 50 years. Essential hypertension was defined as a previous medical diagnosis or receiving treatment, or blood pressure > 140/90 mmHg according to Euro- pean society of HTN and the European society of cardiology (ESH/ESC) guidelines 2013.

Exclusion criteria: Obesity. Diabetes mellitus.Chronic infection. Chronic inflammatory diseases. Renal diseases which associated with increase urinary KIM-1 level including ischemic tubular injury, toxic tubular injury, renal cell carcinoma, polycystic kidney disease and cyclosporine nephrotoxicity. Severe heart and liver failure and secondary hypertension.

All participants were subjected to the followings: History taking , Clinical examination and anthropometric measures including Body mass index (BMI), ECG, and Abdominal ultrasound. Blood samples for Fasting, 2 hours post prandialblood glucose, renal function, Serum albumin, total protein level, cholesterol and triglycerides level. Estimated GFR by MDRD equation (Modification of Diet in Renal Disease. Detection of micro albuminuria and Estimation of urinary KIM-1 by ELIZA method. Urine analysis and 24 h urine

collection.

Statistical analysis was done by using" SPSS" statistical package for the social sciences version 22. pearson correlation were used for detection of association. Multiple linear regression for detection of factors affecting certain outcome. MedClac programme was used for performance of Roc Curve analysis for predication of KIM-[1].

Results: The present case control study was conducted on 120 selected persons from hypertension out-patient's clinic, Minia University Hospital. Our study included 80 patients already diagnosed as having Essential hypertension and were classified into two groups according to duration of hypertension: Group (A): forty patients with a disease duration less than 5 years. Group (B): forty patients with a disease duration more than 5 years. Group (C): forty healthy normal volunteer as a control group.

Table (1): Comparison between group A, B & C regarding e-GFR, micro albuminuria & KIM-1 .

	Group A (hypertensive patients < 5 years n=40)	Group B (hypertensive patients >5 years n=40)	Group C (control) n= 40	p – value			
				general	A&B	A&C	B&C
GFR(ml/min) Range, Mean ± SD	90-122 101.4±8.7	90-119 100.8±7.9	90-135 118±9.08	<0.001	0.939	<0.001	<0.001
micro-albuminuria (mg/24 h) Range, Mean ± SD	5-200 42.6±63.9	15-222 144.6±65.1	2-10 6.02±2.4	<0.001	<0.001*	0.007*	<0.001
KIM-1 (ng/mL) Range Mean ± SD	40-120 59.8±15.9	100-140 119.1±12.4	2-19 11.3±4.6	<0.001	<0.001*	<0.001	<0.001

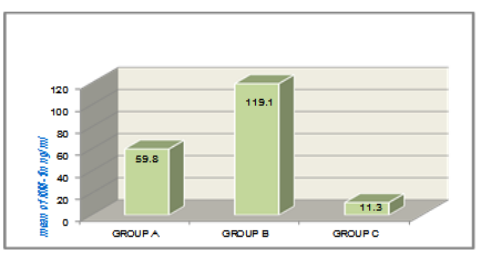

Figure (1): Comparison of KIM-1 among groups A, B & C it shows a statistically very highly significant <0.001) beteween the three groups.

Table 2: Comparison between proteinuric, non proteinuric & control groups regarding KIM-1 level. It shows statistically very highly significant P- value <0.001

	Proteinuric group (n: 48)	Non Proteinuric group (n: 32)	Control (n: 40)	General p value	Proteinuric and Non Proteinuric p value	Proteinuric and control p value	Non Proteinuric and control p value
KIM-1 (ng/mL) Mean ± SD	108.2±26.5	61.3±18.8	11.3±4.6	<0.001*	<0.001*	<0.001*	<0.001*

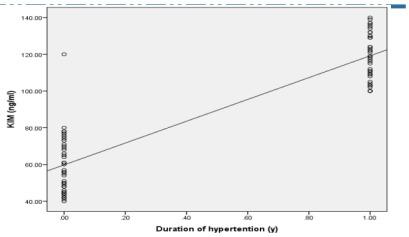

Figure (2): Correlation between KIM-1 and duration of hypertention (stronge positive correlation r is 0.903).

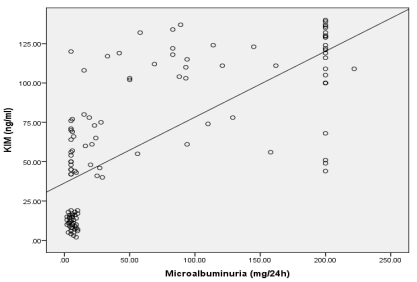

Figure (3): Correlation between KIM-1 and micro albuminuria (moderate positive correlation r is 0.719).

Table (3) Linear regression analysis for factors affecting KIM level among studied groups: it showed that duration of hypertension is the main factor affecting KIM-1 (B=62.4, P <0.001). *Calculated by the standard method of multiple linear regression (R^2 = 0.88)

Independent variables	ß	P-value
Duration of HTN	62.4	<0.001*
BMI	-2.5	0.004*
FBG	0.42	0.02*
Creatinine	9.8	0.6
Drug	1.6	0.4
GFR	0.33	0.2
DBP	-0.21	0.3
Urea	-0.18	0.3
Two hour post prandial	-0.14	0.6
SBP	0.053	0.6
BP control	0.023	0.9
micro albuminuria	0.019	0.5

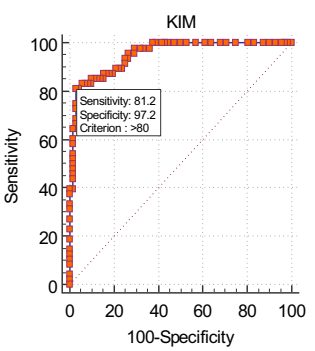

Figure 4, Receiver operating characteristic (ROC) curve analysis of the KIM-1 values showing KIM value in predicting micro albuminuria in patients with hypertensive nephropathy, AUC was 0.95. KIM value 80 ng/ml was the best cut-point that gave the sensitivity of 81.2% and specificity of 97.2%.

Discussion

Traditional serum biomarkers used to diagnose acute and chronic renal dysfunction, such as BUN and creatinine, are insensitive, nonspecific, and typically rise late in the disease process(13).

Estimation of GFR by serum creatinine-based equations is the most precise method to estimate the decline of renal function or the effect of a treatment Hence significant effort has been devoted to identify blood or urine biomarkers that can better diagnose and assess patients' risk for incident AKI and worsening CKD. These include biomarkers of inflammation (Interleukin-18), biomarkers of structural kidney tubule damage such as neutrophil gelatinase associated lipocalin (NGAL) and kidney injury molecule- (KIM-1)(14). KIM-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. It mediates epithelial cell phagocytosis of apoptotic cells, which protects the kidney after acute injury by down regulating immunity and inflammation(15). KIM-1 in the urine is highly specific for kidney injury[16].

Essential hypertension is a widespread disease. Hypertensive nephropathy with early renal damage often occurs without symptoms[17].

In our study systolic & diastolic BP showed very highly statistical significance between the patient groups (A & B) and the control group (C) with statistical insignificance among the patient groups (A & B), This was consistant with Zulu et al., 2016(18) who reported that there was a significant difference in blood pressure levels (systolic and diastolic) between hypertensive and non-hypertensive participants.

Estimated GFR levels were lower in patient groups (A & B) compared with control group (C) while micro albuminuria level was higher in patient groups (A & B) compared with control group (C) this is in agreement with Kadiolgu et al., 2016(19). This could be explained by that, hypertension may differentially affect GFR and urinary albumin excretion by increasing intra glomerular pressure and, thereby, increase urinary excretion of albumin.

Zacharias et al., 2012(20) reported that Increased MAU lead to an increased risk of kidney disease progression and death,. Micro albuminuria showed moderate negative correlation with blood pressure control r is -0.556. This is inconsistnt with Bakris et al., 2010(21) who reported that reduction in blood pressure itself has beneficial effects on urinary albumin excretion regardless of antihypertensive drugs used.

In our study urinary KIM-1 level was higher in patient groups (A & B) compared with control group ©. This is consistant with (Vaidya et al., 2010)(22) who reported elevated KIM-1 level in all participating renal disease patients and is higher than controls, however Zulu et al., 2016(18) & Kadiolgu et al., 2016(19) reported that there was no difference in KIM-1 concentration between hypertensive and non-hypertensive individuals.

In our study it was found that KIM-1 was elevated despite normal urinary albumin excretion in the Normo albuminuric subgroup. This is consistant with Peralta et al., 2012(23) who reported that urinary KIM-1 level is associated with future risk of kidney disease independent of albuminuria, it was suggested that elevated urinary KIM-1, which can be detected before albuminuria, is a marker of the tubular injury that develops before glomerular damage (Tekce et al., 2014)[24].

Castillo-Rodriguez et al., 2017(25) reported that urinary KIM-1 was higher in patients with proteinuria and normal renal function than in non-proteinuric individuals.

In our work KIM-1 had strong positive correlation to the duration of hypertension r is (0.903), This is consistant with Kadiolgu et al., 2016(19) who reported positive correlation between KIM-1 level and duration of hypertension. this finding suggest that, urinary KIM-1 level can be used as an early marker of kidney injury in hypertensive nephropathy independent of albuminuria. Our study revealed that urinary KIM-1 level had moderate positive correlation with micro albuminuria r is 0.588 and this is consistant with Zulu et al., 2016[18].

In the present study it was found that KIM-1 had moderate negative correlation with GFR r is -0.539, this is consistant with Tian et al., 2017[26].

Also, we found that KIM-1 had moderate negative correlation with blood pressure control r is -0.556 this is consistant with Kadiolgu et al., 2016(19) who reported that KIM-1 level is lower in controlled hypertensive patients than uncontrolled ones in the patient group this could be explained by controlling of blood pressure may affect KIM-1 level Our result revealed that micro albuminuria is moderately correlated to duration of hypertension r is 0.625 this is consisant with Dayal et al., 2014(27) who reported that 80% of the patients having hypertension for more than 7.5 years had micro albuminuria demonstrating increased frequency with increasing duration of hypertension. Also in our study, Micro albuminuria showed moderate positive correlation with SBP & DBP r is 0.592 and 0.544 respectively this is consistant with Abdallah et al., 2012(28). This was also evident in models that involved a group of patients with very poorly controlled blood pressure were strongly associated with micro albuminuria.

Our study showed that GFR had a moderate positive correlation with blood pressure control r is 0.616 and moderate negative correlation with SBP & DBP (r is -0.589 & -0.587) respectively, this could be explained by that, elevation of blood pressure increases intra glomerular pressure and resultant injury to the epithelial lining leading to leakage of albumin and deterioration of GFR.

In our study Linear regression analysis for factors affecting KIM level among studied groups showed that, duration of hypertension is the main factor affecting KIM-1 (B=62.4, P <0.001). Also, it was found that the KIM value that can predict proteinuria among patients with hypertensive nephropathy was 80 ng/ml with 81.2% sensitivity and 97.2% specificity.

Conclusion : urinary KIM-1 level is higher in hypertensive patients than control group. Duration of hypertension is the main factor affecting KIM-1. It has a sensitivity of 81.2% and specificity of 97.2% in predicting micro albuminuria in hypertensive nephropathy. Urinary KIM-1 can be detected before micro albuminuria, so it can be used as an early marker of kidney injury in hypertensive patients.

REFERENCES :

1- Leung A, Daskalopoulou S, Dasgupta K et al., 2017. Guidelines Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. Canadian Journal of Cardiology 33 (557):76.
2- O'Shea P, Griffin T and Fitzgibbonc M 2017. Hypertension: The role of biochemistry in diagnosis and management. Clinica Chimica Acta (465):131 –43.
3- El Mawardy R and Okba A 2017. Antihypertensive treatment and blood pressure control in patients with hypertension in daily clinical practice: A cross-sectional, multicentre, observational study in Egypt. Current Medical Research and Opinion (33): 39-45.
4- Hasan D, Emeash A, Mustafa S et al., 2014. Hypertension in Egypt: A Systematic Review, Current Hypertension Reviews (10): 134-41.
5- Ibrahim MM 2014. The Egyptian Hypertension Society: Egyptian hypertension guidelines. The Egyptian Heart Journal. 66(2):79-132.
6- Farag YM, Kari JA and Singh AK 2012. Chronic Kidney Disease in the Arab World: A Call for Action. Nephron Clin Pract (121):c120-3.
7- El Minshawy O and Osman A 2010. Albuminuria Predicts Kidney Function Outcome in Egyptian Essential Hypertensive Patients. Int J Nephrol Urol; 2(1): 224 – 33.
8- Yin C and Wang N 2016. Kidney injury molecule-1 in kidney disease, RENAL FAILURE. 38 (10): 1567–73.
9- Miao J, Friedman E, Wu AHB et al., 2017. Clinical utility of single molecule counting technology for quantification of KIM-1 in patients with heart failure and chronic kidney disease, Clin Biochem. 50 (16-17):889-95.
10- Ogrizovic SS, Bojic S, Basta-Jovanovic G et al., 2013. Tissue Kidney Injury Molecule-1 Expression in the Prediction of Renal Function for Several Years after Kidney Biopsy. 35 (5): 567–72.
11- Liu X, Guanb Y, Xu S et al., 2016. Early Predictors of Acute Kidney Injury: A Narrative Review. Kidney Blood Press Res (41): 680-700.
12- Rysz J, Gluba-Brzózka A, Franczyk B et al., 2o17. Novel Biomarkers in the Diagnosis of CKD and the Prediction of Its Outcome. Int J Mol Sci. 18(8): E1702.

13- Vanmassenhove J, Vanholder R, Nagler E et al., 2013. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 28(2):254-73.
14- Araujo M and Doi SQ 2017. Editorial: Biomarkers in CKD. Front Med (Lausanne). 4:168.
15- Zhang Z, Cai CX, 2016. Kidney injury molecule-1 (KIM-1) mediates renal epithelial cell repair via ERK MAPK signaling pathway. Mol Cell Biochem. 416(1-2):109-16.
16- Boghdady I, EL Naggara M, Emara M et al., 2013. Kidney injury molecule-1 as an early marker for acute kidney injury in critically ill patients, Menoufia Medical Journal. (26):98–104.
17- Wang XC, Liu CH, Chen YJ et al., 2013. Clinical and pathological analysis of the kidney in patients with hypertensive nephropathy. Exp Ther Med. 6(5):1243
18- Zulu M, Kaile T, Kantenga T et al., 2016. Kidney injury molecule-1 and micro albuminuria levels in Zambian population biomarkers of kidney injury. Pan African Medical Journal (13) 24:54.
19- Kadioglu T, Uzunlulu M, Yigit Kaya S et al., 2016.Urinary kidney injury molecule-1 levels as a marker of early kidney injury in hypertensive patients. Minerva Urol Nefrol. 68(5):456-61.
20- Zacharias JM, Young TK, Riediger ND et al., 2012. Prevalence, risk factors and awareness of albuminuria on a Canadian First Nation: A community -based screening study.Biomed central public Health. (12):290.
21- Bakris GL, Sarafidis PA, Weir MR et al., 2010. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. Lancet. 375 (9721):1173–81.
22- Vaidya VS, Ozer JS, Dieterle F et al., 2010. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. Nat Biotechnol. 28(5):478-85.
23- Peralta CA, Katz R, Bonventre JV et al., 2012. Associations of urinary levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) with kidney function decline in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 60(6):904-11.
24- Tekce BK, Tekce H, Aktas G et al., 2014. Evaluation of the Urinary Kidney Injury Molecule-1 Levels in Patients With Diabetic Nephropathy Clin Invest Med. 37 (6): 377-83.
25- Castillo-Rodriguez E. Fernandez-Prado R. Martin-Cleary C et al., 2017. Kidney Injury Marker 1 and Neutrophil Gelatinase-Associated Lipocalin in Chronic Kidney Disease, Nephron .136 (4):263-7.
26- Tian L, Shao X, Xie Y et al., 2017. Kidney Injury Molecule-1 is Elevated in Nephropathy and Mediates Macrophage Activation via the Mapk Signalling Pathway. Cell Physiol Biochem. (41):769-83.
27- Dayal A, Raval B and Trivedi NJ 2014. Microalbuminuria In Essential Hypertension. NJIRM. 5(1).
28- Abdullah AA, 2012. Prevalence of and clinical characteristics associated with microalbuminuria in hypertension. PhD thesis, University of Glasgow.