

Medicine

KEYWORDS:

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



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Mahmoud Hassan S Khedr

Internal Medicine Dep., Faculty of Medicine, Minia University, Egypt.

Eglal M.S Hamed*

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

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.

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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 prandial blood 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

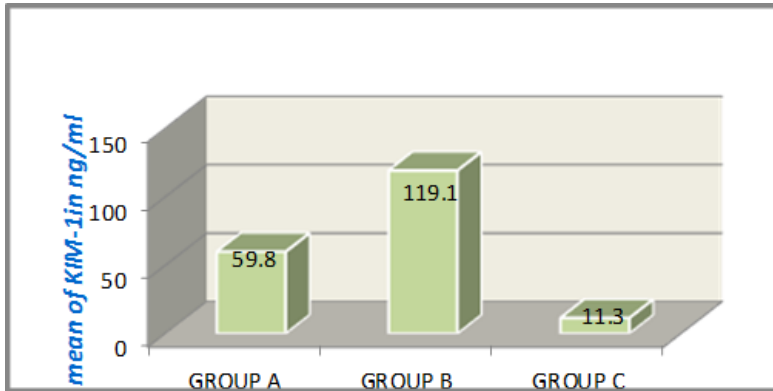


Figure (1): Comparison of KIM-1 among groups A, B & C it shows a statistically very highly significant <0.001) between the three groups.

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*

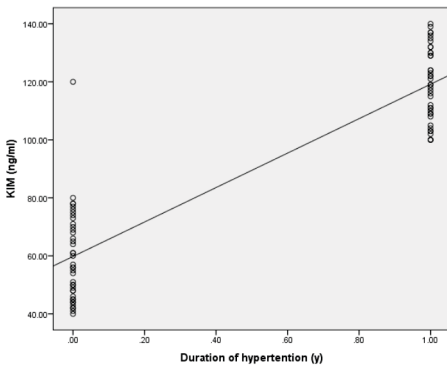


Figure (2): Correlation between KIM-1 and duration of hypertension (stronge positive correlation ris is 0.903)

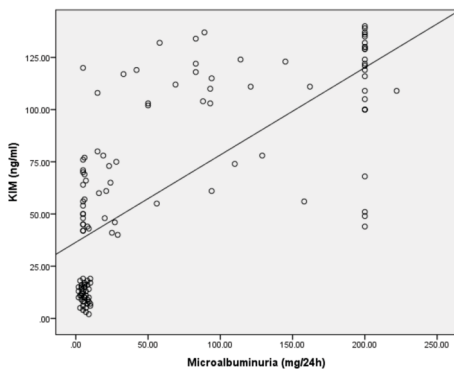


Figure (3): Correlation between KIM-1 and micro albuminuria (moderate positive correlation ris is 0.719).

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 (R² = 0.88)

Independent variables	β	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

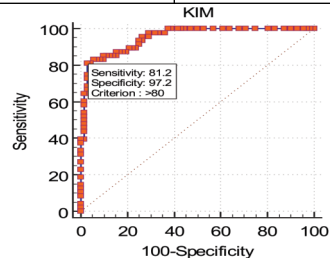


Figure 4, Receiver operating characteristic (ROC) curve analysis of the KIM-1 values showing KIM value in predicting micro

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 consistent 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 inconsistent 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 consistent 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 consistent 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 consistent 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 consistent 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 consistent 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 consistent 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 consistent 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 consistent 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.

المخلص العربي

قيمة مستوي جزئ اصابة الكلي-1 في البول كعلامة لحدوث اعتلال الكلية في مرضى ضغط الدم المرتفع

محمود حسن سيد خضرم, إجلال محمد شوقي حامد, صفاء محمد حسين على, هند محمد مؤنس و ايمان سامح محمد

قسم الأمراض الباطنية, قسم الباثولوجيا الاكلينيكي, قسم الصحة العامة - كلية الطب - جامعة المنيا

الهدف من هذه الدراسة هو قياس مستوي جزئ اصابة الكلى -1 في مرضى ارتفاع ضغط الدم كمؤشر لحدوث اصابة مزمنة بالكلى وكذلك دراسة علاقته بالحالة الاكلينيكية والعلامات البيوكيميائية والمدة الزمنية للإصابة بالمرض.

وقد كانت هذه دراسة وصفية أجريت في عيادة أمراض ضغط الدم المرتفع في الفترة من نوفمبر 2016 إلى إبريل 2017 بمستشفى المنيا الجامعي, كلية الطب, جامعة المنيا.

وقد تم تقسيم الافراد المدرجين في هذه الدراسة إلى ثلاثة مجموعات: المجموعة الأولى (المرضى الذين يعانون من مرض ارتفاع ضغط الدم لمدة تقل عن خمس سنوات), وقد شملت هذه المجموعة 40 مريضاً, 14 (35%) من الذكور و 26 (65%) من الإناث, وتراوحت أعمارهم من 30 إلى 50 عاماً, والمجموعة الثانية (المرضى الذين يعانون من مرض ارتفاع ضغط الدم لمدة تزيد عن خمس سنوات), وقد شملت هذه المجموعة 40 مريضاً, 15 (37.5%) من الذكور و 25 (62.5%) من

الإناث، وتراوحت أعمارهم من ٣٠ إلى ٥٠ عاماً، أما المجموعة الضابطة فقد شملت ٤٠ شخصاً من الأصحاء، ٢١ (٥٢,٥٪) من الذكور و١٩ (٤٧,٥٪) من الإناث. تراوحت أعمارهم من ٣٠ إلى ٥٠ عاماً.

وقد تم إخضاع جميع الأفراد الذين شملتهم هذه الدراسة إلى الآتي: أخذ التاريخ الدقيق للمرض، والفحص الإكلينيكي الكامل، والدراسات المعملية والتي شملت: (مستوى السكر بالدم، اختبارات وظائف الكلى، مستوى الدهون بالدم واختبارات وظائف الكبد) تقدير معدل الترشيح الكبيبي، الكشف عن وجود زلال دقيق بالبول، الكشف عن وجود جزيء إصابة الكلى -١، فحص البطن بالموجات فوق الصوتية، وتخطيط كهربائي للقلب.

وقد أظهرت هذه الدراسة انخفاضاً ملحوظاً في معدل الترشيح الكبيبي لدى المرضى الذين يعانون من مرض ارتفاع ضغط الدم بدلالة إحصائية عالية وذلك مقارنة بالمجموعة الضابطة وارتفاعاً ملحوظاً في مستوى الزلال الدقيق بالبول وبمستوى جزيء إصابة الكلى -١ لدى المرضى الذين يعانون من مرض ارتفاع ضغط الدم بدلالة إحصائية عالية وذلك مقارنة بالمجموعة الضابطة.

وقد أظهرت الدراسة أن مرضى ارتفاع ضغط الدم المصاب بوجود زلال دقيق بالبول لديهم ارتفاعاً ملحوظاً بمستوى جزيء إصابة الكلى -١ بدلالة إحصائية عالية وذلك مقارنة بمرضى ارتفاع ضغط الدم الغير مصاب بوجود زلال دقيق بالبول.

وقد أظهرت الدراسة وجود علاقة إيجابية قوية بين مستوى جزيء إصابة الكلى -١ والفقرات الزمنية لارتفاع ضغط الدم وعلاقة إيجابية متوسطة بين مستوى جزيء إصابة الكلى -١ ومستوى الزلال الدقيق بالبول ومستوى ضغط الدم الانقباضي والانبساطي وعلاقة سلبية متوسطة بين مستوى جزيء إصابة الكلى -١ ومعدل الترشيح الكبيبي والنباض ضغط الدم.

كما أظهرت الدراسة وجود علاقة إيجابية متوسطة بين مستوى الزلال الدقيق بالبول والمدة الزمنية لارتفاع ضغط الدم ومستوى ضغط الدم الانقباضي والانبساطي وعلاقة سلبية متوسطة بين مستوى الزلال الدقيق بالبول والنباض ضغط الدم. بينما أظهرت الدراسة وجود علاقة إيجابية متوسطة بين معدل الترشيح الكبيبي والمدة الزمنية لارتفاع ضغط الدم وعلاقة سلبية متوسطة بين معدل الترشيح الكبيبي ومستوى ضغط الدم الانقباضي والانبساطي.

وأظهرت الدراسة أن المتنبئ الرئيسي لمستوى جزيء إصابة الكلى -١ هو المدة الزمنية لارتفاع ضغط الدم بنسبة تصل إلى ٤٢,٤٪ وذلك باستخدام تحليل الانحدار الخطي للعوامل التي تؤثر على مستوى جزيء إصابة الكلى -١ بين المجموعات المدروسة.

وقد أظهر منحنى خصائص المستقبل التشغيلية لتحديد قيمة مستوى جزيء إصابة الكلى -١ التي يمكن من خلالها التنبؤ بوجود زلال دقيق بالبول لدى مرضى اعتلال الكلية نتيجة ضغط الدم المرتفع أن ٨٠ نانوجرام لكل مل هو قيمة مستوى جزيء إصابة الكلى -١ التي أظهرت نسبة ٢,٨١٪ حساسية و ٩٧,٩٪ تخصصية في التنبؤ بوجود زلال دقيق بالبول لدى مرضى اعتلال الكلية نتيجة ضغط الدم.

ومن خلال هذه الدراسة يمكننا استنتاج الآتي:

أن مرضى ضغط الدم المرتفع لديهم ارتفاعاً ملحوظاً بمستوى جزيء إصابة الكلى -١ مقارنة بالأصحاء وأن المدة الزمنية لارتفاع ضغط الدم المزمن هي أقوى متنبئ بوجود ارتفاع بمستواه ومن الممكن الكشف عن وجوده قبل ظهور زلال البول في هؤلاء المرضى لذلك يمكن الكشف عن مستوى جزيء إصابة الكلى -١ كعلامة مبكرة لحدوث اعتلال الكلية في مرضى ضغط الدم.

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