Research Article

Kidney injury molecule-1 as a biomarker for prediction of kidney injury in pre-eclampsia

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Abstract
Background: Preeclampsia has remained a public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally, Kidney injury with proteinuria is a characteristic feature of preeclampsia, yet the nature of injury in specific regions of the nephron is incompletely understood **Aim and objectives**: The aim of the present study is to evaluate the role of kidney injury molecule-1 as a biomarker for predicting kidney injury in preeclampsia, **Subjects and methods:** This is a case control study was carried out at the department of obstetrics and gynecology, Minia maternity university hospital during the period from September 2018 to March 2019, the study was conducted on 90 patients were be enrolled in to the study and divided into two groups, **Results:** the results of the study revealed that there is high significant correlation between kidney injury molecule -1and severity of preeclampsia, **Conclusion**: there is an increase in the urinary level of kidney injury molecule-1 in PE, implicating their possible value as biomarkers of kidney injury,
Keywords: Biomarkers, Kidney, Injury, Pre-Eclampsia, Molecule -1.

Introduction
During normal pregnancy, significant physiologic mechanisms that alter systemic and renal hemodynamics play an important role in the renal response to changes in fluids and electrolytes[(1)]. Glomerular filtration rate (GFR) rises immediately after conception, reaching 50% above baseline and resulting in significant hyperfiltration in second trimester; then GFR falls by 20% returning to antepartum levels within 3 months of delivery[(2)].

Pre-eclampsia is a pregnancy-related hypertensive disorder occurring usually after 20 weeks of gestation which is characterized by elevated blood pressure, proteinuria and different organ systems damage including the kidney, liver, brain, heart and lungs. In 30% of the cases, the disease may cause placental insufficiency, leading to intrauterine growth restriction or fetal death[(3)].

Pre-eclampsia has remained a public health threat in both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally[(4)].

It affects 2–5% of pregnancies in Western countries and complicates up to 10% of pregnancies in the developing countries, where emergency care is frequently inadequate or even lacking[(5)].

Kidney injury with proteinuria is a characteristic feature of pre-eclampsia, yet the nature of injury in specific regions of the nephron is incompletely understood. Glomerular barrier dysfunction, characterized by glomerular endotheliosis is a possible pathogensis[(6)].

However, inflammation and injury to the proximal tubule also contributes to disease pathogenesis in many kidney disorders[(7)].

Although the cause of pre-eclampsia is incompletely understood, [8], complement activation is central to the systemic inflammatory response in pre-eclampsia, possibly in response to apoptotic or necrotic trophoblast debris at the placental interface and in systemic circulation[9].
Marked urinary excretion of complement components in severe pre-eclampsia suggests that complement-mediated kidney injury is a key feature of disease[10].
The kidney injury molecule-1 (KIM-1) is produced by cells of the renal tubular epithelium and interstitial macrophages[11].

The level of KIM-1 is low in concentration during normal physiological state, but its expression is significantly elevated in kidney diseases[12].
An increase in the level of urinary KIM-1 concentrations is indicative of ischemic injury of the kidney[13].

IL-18 is a biomarker specific for kidney injury depicting ischemic injury of the proximal tubules. In the absence of kidney injury, only a trace of urinary IL-18 is seen, yet its concentration is raised by several folds during injury[14].

Aim of the Work

The aim of this study is to evaluate the role of kidney injury molecule-1 as a biomarker for predicting kidney injury in pre-eclampsia.

Patients and Methods

I- Setting:

This study was carried out at the department of obstetrics and gynecology, Minia maternity university hospital during the period from September 2018 to march 2019 .

II-Funding:

This project was locally funded from Minia University as a part of covering the expenses of the candidate and carried out under shared supervision between. Prof. Dr / Mohamed Hany Mosabeh, Dr. Ahmed Rabie Abd El-Raheim and Dr / Ahmed Mohamed Abdelgany using the equipments in the department.

III-Ethical issues:

The ethical committee of the department of Obstetrics & Gynecology at Minia College of medicine approved the study (Registration No: **MUEOB0026**)
All Participants had signed a written informed consent after they have been made aware of the purpose of the study, interventions, outcome and possible complications.

IV -Plan of the study:

Our study will be conducted at Minia Maternity University hospital in the outpatient clinic starting from September 2018.
In this study 90 patients will be enrolled in to the study and will be divided into three groups,
Group A: included 45 women who are normotensive.
Group B: included 45 women who are pre-eclamptic.

Inclusion criteria:

1. Patients with singleton pregnancy of 20 ws gestation and more.
2. Age between 18-35yrs.
3. Preeclamptic patient.
4. Eclamptic patient.

Pregnant women with preeclampsia and normal pregnant women will be enrolled from the Department of Gynecology and Obstetrics, Minia university. Preeclampsia was defined as systolic blood pressure (SBP) 140mmHg or diastolic blood pressure (DBP) 90 mmHg after 20 weeks of gestation, accompanied by proteinuria 41þ by dipstick in a random urine analysis or 300mg/24h with no evidence of urinary tract infection.

Exclusion criteria:

1- Patients with multiple gestations.
2- Pregnancies with major fetal anomalies.
3- Chronic urinary tract infection.
4- Chronic kidney diseases.
5- Gestational hypertension.

Results

Table (1): Demographic data in between the studied groups:

Variable	Control N=45	Preeclampsia N=45	t-test	P value
Age: (months):				
Mean ± SD Range	25.4±14.4 (18-33)	25.45±14.9 (19-35)	0.126	0.908 (NS)
Gravidity:				
Median Range	1 (1-2)	1 (1-2)	U 512.5	0.453
Parity:				
Median Range	1 (0-2)	1 (0-2)	U 534.2	0.367
Abortion:				
Median Range	0 (0-1)	0 (0-1)	U 530.5	0.441

U is for Mann Whitney test, p value is significant if <0.05

This table shows that there is no statistical significant difference between the two studied groups as regard baseline demographic data.

Table (2): Maternal anthropometric measures in between the studied groups:

Variable	Control N=45	Preeclampsia N=45	t-test	P value
Weight (kg):				
Mean ± SD	80.4±11.9	82.1±10.2	2.9	**0.043 (S)**
Height (cm):				
Mean ± SD	161.8±5.4	161.7±5.7	0.09	0.928
BMI(KG/m^2)				
Mean ± SD	26.8±3.7	28.9±2.7	2.7	**0.047 (S)**

This table shows that there is significant difference between the studied groups as regard weight and BMI while there is no significant difference between them as regard height.

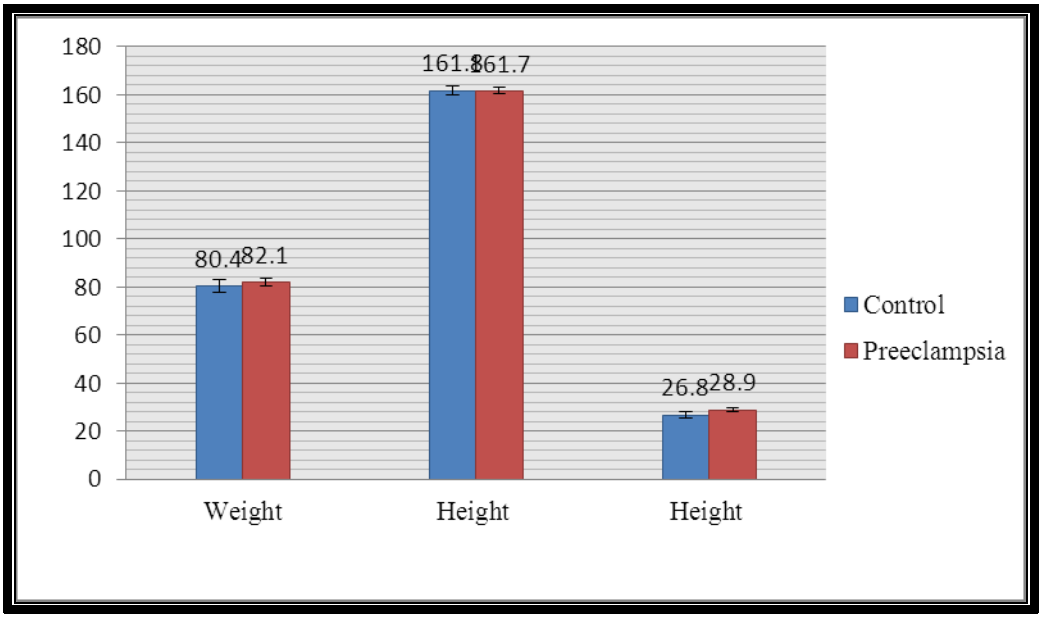

Fig.(1) Maternal anthropometric measures in between the studied groups

Table (3): clinical and laboratory data in between the studied groups:

Variable	Control N=45	Preeclampsia N=45	t-test	P value
Creatinine:				
Mean ± SD Range	1.1±0.1 0.9-1.2	1.7±0.35 1.5-3.4	11.3	**<0.001 (HS)**
Haemoglobine:				
Mean ± SD Range	11.87±1.51 9.4-13.3	11.84±1.56 9.1-13.1	0.124	0.911

Discussion

Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually every organ system. Preeclampsia is much more than simply gestational hypertension with proteinuria, appearance of proteinuria remains an important objective diagnostic criterion, Preeclampsia is a major cause of morbidity and mortality in pregnant women and infants. It is defined as new-onset hypertension accompanied by proteinuria (or other end-organ dysfunction) occurring after 20 weeks' gestation in a previously normotensive woman[(6)].

Preeclampsia is a multifactorial progressive disorder characterized by hypertension and proteinuria during the 2nd half of pregnancy or afterwards. Kidney injury is a characteristic feature of preeclampsia. Kidney injury with proteinuria is a characteristic feature of preeclampsia, yet the nature of injury in specific regions of the nephron is incompletely understood. Glomerular barrier dysfunction, characterized by glomerular endotheliosis[(5)] and podocyte loss has been emphasized in severe preeclampsia because marked albuminuria is a hallmark feature of disease[(6)].

Kidney injury in preeclampsia is most commonly defined by the total excretion of urinary protein in 24 hours or by the ratio of total urine protein to creatinine in a random urine collection. However, the validity of standard urinary protein measurements for

the diagnosis of preeclampsia has been questioned, partly because the extent of proteinuria in preeclampsia does not correlate well with disease severity[9].

In preeclampsia, the integrity of the glomerular basement membrane may be impaired by increased serum levels of soluble fms-like tyrosine kinase-1, which sequesters vascular endothelial growth factor[10], Urinary excretion of podocytes from the glomerulus and loss of negative charge density at the glomerular membrane also contribute to filtration of albumin in the urine. Filtered albumin, or compounds carried by albumin, may trigger inflammation with direct injury to proximal tubule cells. Albumin may also compete for reabsorption at the proximal tubule with low-molecular-weight proteins such as B2M, cystatin C, and NGAL. Alternatively, filtered proteins may be excreted in the urine because of impaired proximal tubule reabsorption of other cause [12].

The kidney injury molecule-1 (KIM-1) is produced by cells of the renal tubular epithelium and interstitial macrophages[13]. The level of KIM-1 is low in concentration during normal physiological state, but its expression is significantly elevated in kidney diseases[14]. An increase in the level of urinary KIM-1 concentrations is indicative of ischemic injury of the kidney[13].

The aim of the present study is to evaluate the role of kidney injury molecule-1 as a biomarker for predicting kidney injury in preeclampsia.

This is a case control study was carried out at the department of obstetrics and gynecology, Minia maternity university hospital during the period from September 2018 to March 2019, the study was conducted on 90 patients were be enrolled in to the study and divided into two groups,

Group A: included 45 women who are normotensive.

Group B: included 45 women who are preeclamptic.

Conclusion

In conclusion, our results demonstrated an increase in the urinary level of kidney injury molecule-1 in PE, implicating their possible value as biomarkers of kidney injury.

Recommendation

- Further studies on large geographical scale and larger sample size to emphasize our conclusion
- Further studies on further biomarkers that can be included in detection of acute kidney injury in preeclampsia and compare sensitivity of single and combined biomarkers.
- As a direct extension of this research, additional studies could be performed to confirm the independent association between several maternal characteristics in this study and the risk of AKI in pregnancy.
- Additional research is needed to establish a method of early and specific diagnosis of AKI in pregnancy, perhaps using renal biomarkers that are independent of serum creatinine, a late indicator of acute kidney injury in pregnancy.

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