Urinary Sodium to Creatinine and Calcium to Creatinine Ratios as a Marker in Diagnosis of Preeclampsia

Protocol of Thesis

Submitted for partial fulfillment of Master Degree

In Obstetrics and Gynecology

By

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Samar Sobh Mohammad Ghozi

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List of Abbreviations

Abb	Meaning
ACOG	*American college of obstetric*
ANP	*Atrial natriuretic peptide*
BMI	*Body man index*
BNP	*Brian natriuretic peptide*
Ca	*Calcium*
Ca / Cr	*Calcium to creatinine ratio*
CEC	*Circulating endothelial ratio*
Cr	*Creatinine*
DBP	*Diastolic blood pressure*
DOC	*Deoxy corticosterone*
EMPS	*Endothelial micro particles*
ET-1	*Endothelin – 1*
GFB	*Glomerular filtration barrier*
GFR	*Glomerular filtration rate*
HBV	*Hepatitis B virus*
HCV	*Hepatitis C virus*
HIV	*Human Immunodeficiency virus*
HLA	*Human leukocyte antigen*
IL	*InterLukines*
MPGN	*Membrano-proliferative glomerulonephritis*
Na	*Sodium*
Na / Cr	*Sodium to creatinine ratio*
NK	*Natural killer*
NO	*Nitric oxide*
0-CPC	*0- cresol phthalic complexone*
PE	*Pre-eclampsia*
RAAS	*Renin angiotensin aldosterone*
ROC	*Receiver operating curve*
SBP	*Systolic blood pressure*
SD	*Standard deviation*
S ENG	*Soluble endoglin*
TMA	*Thrombotic micro-angiopathy*
TNFα	*Tumor necrosis factor α*
U Pr / Cr	*Urinary protein to creatinine ratio*
VEGF	*Vascular endothelial growth factor*
VSM	*Vascular smooth muscle*

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Introduction

Preeclampsia is defined as systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mm Hg that occurs after 20 weeks of gestation with proteinuria ***(Cunningham FG et al., 2001).***

It complicates 2-8% of all pregnancies ***(Khan et al., 2005),*** it is a multisystem endothelial disease that lead to glomeruloendotheliosis ***(Hennesy, 2011)***, and in severe cases it may lead to renal impairment and failure.

Urine collection over 24 hours is considered the traditional comparator for quantification of proteinuria in pregnancy, when significant proteinuria is defined as proteinuria of 300 mg/day or more ***(Adelberg et al., 2001)***

Patients with hypertension have only < 300mg , those with mild pre-eclampsia have 300 mg to 5gm and those with severe preeclampsia have >5gm of proteinuria. The urine requires refrigeration and its collection is cumbersome, time consuming (for women and ward staff), and potentially misleading if collected inaccurately. Also, it may not be possible to complete the urine collection when delivery occurs, leading to undetermined proteinuria status and an unsubstantiated diagnosis of pre-eclampsia; less than half of women admitted with pre-eclampsia have a 24 hour urine collection sent for analysis ***(Brown et al., 1995).***

Timed collections delay clinical diagnosis and may result in prolonged hospital stay when a hypertensive disorder of pregnancy is being investigated, thereby increasing patient anxiety and healthcare costs.

Because of the disadvantages of 24 hour urine collection, alternatives for the diagnosis of proteinuria in pregnancy have been considered.

These include urinary dipsticks, urine collections over a shorter period, the urinary spot protein: creatinine ratio, and the urinary spot albumin: creatinine ratio. The dipstick is inexpensive, easy to use, and provides a rapid result but has been shown to have low sensitivity and specificity for urinary protein excretion over 24 hours ***(Menzies et al., 2007).***

The urine protein–creatinine ratio has been considered important for predicting proteinuria in pregnant patients. It compares the spot urine protein excretion to the spot urine creatinine excretion, thereby normalizing protein excretion to the glomerular filtration rate. Thus, the urine protein–creatinine ratio is not subject to variation due to hydration status. (***Wongkitisophon et al., 2003).***

Although several studies have shown that the urine protein:creatinine ratio is a predictor of significant proteinuria ***(Valerio et al., 2005)*** , others have found a weaker value of this test for this purpose (***AlRA et al., 2004).***

Nevertheless, the appropriateness of the urine protein:creatinine ratio as a screening test for proteinuria is

still unclear, in part because of the paucity of large studies on proteinuria in pregnant women with hypertension.

The kidney is the organ most likely to manifest endothelial injury related to preeclampsia.

Glomerular filtration rate (GFR) decreases by 30 to 40 percent in preeclampsia compared to pregnant normotensive controls; renal plasma flow also decreases, but to a lesser degree. The plasma creatinine concentration is generally normal or only slightly elevated (1.0 to 1.5 mg/dL [88 to 133 micro mol /L]). A rising creatinine and oliguria, i.e: urine output <500 mL/24 hours, indicates severe disease and results from renal vasoconstriction and sodium retention due to reduced plasma volume and systemic vasoconstriction ***(Krane et al., 1998)***.

Hyperuricemia and hypocalciuria are also observed ; the mechanisms for these changes are not clear ***(Moran et al., 2004).*** The rise in serum uric acid concentration is thought to reflect increased proximal sodium resorption and, secondarily, urate reabsorption induced by renal ischemia. Other possible mechanisms for hyperuricemia in preeclampsia include underlying metabolic syndrome, tissue damage, oxidative stress, and inflammation ***(Powers et al., 2006).***

Several abnormalities of calcium metabolism have been described in women with this disease. Many investigators have written about hypocalciuria in preeclampsia compared with normotensive pregnant women ***(Ingec, 2006 and Ramos, 2000)***.

Based on this evidence, the calciuria measurement has been suggested as a diagnostic test for preeclampsia.

Some studies have found reduced natriuria in preeclampsia , probably related to the hypocalciuria process. Because of renal involvement, reabsorption of sodium linked to calcium in the ascending loop of Henle has been described***(McGrowde and William, 2009).***

The tests used for the early diagnosis of preeclampsia are, among others, Doppler ultrasound assessment of maternal and fetal circulation, uric acid concentration , and calcuria levels. Studies using measurements of 24-h urinary calcium excretion have documented decreased excretion in women with preeclampsia or who developed the disease sometime after the collection of urine.

Some investigators have evaluated the calcium -to -creatinine ratio as a rapid method of measuring urinary calcium excretion.they found a lower urinary calcium-to-creatinine ratio (0.17 ± 0.03) in preeclamptic women compared with normotensive women (0.45 ± 0.08) (***McGrowder D and Williams, 2009).***

Depending on the studies suggested that calcuria level in 24 hour urine sample collection can be replaced by spot urine for calcium to creatinine ratio , naturia level also can be measured by sodium to creatinine ratio aiming to use both as a diagnostic tests for preeclampsia.

Aim of the work

The Aim Of This Work Is To:

Assess if urinary calcium to creatinine and sodium to creatinine ratios can be used as a marker in diagnosis of preeclampsia.

Research Question:

In women with preeclampsia , are calcium to creatinine ratio and sodium to creatinine ratio lower than the corresponding levels in normal pregnant women?

Hypothesis:

In women with preeclampsia , calcium to creatinine ratio and sodium to creatinine ratio may be low compared to levels in normal pregnancies.

Patients and Methods

Recruitment and Eligibility:-

Site:

Ain Shams University Maternity Hospital.

Type of the study:

Cross Sectional Study.

Subject:

All study will include 135 pregnant women during their third trimester and will be separated into three groups :-

Group 1: (Severe preeclampsia) n = 45 .

Group 2: (Mild preeclampsia) n = 45 .

Group 3: (Normal pregnancy) n = 45 .

Criteria for diagnosis of severe preeclampsia:

- Systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mm Hg on two occasions at least four hours apart while the patient is on bed rest.
- Severe proteinuria (≥5 grams / day).
- Platelets count <100,000 cells /microL.

- Progressive renal insufficiency (serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration in the absence of other renal disease ***(ACOG, 2013).***

Criteria for diagnosis of mild preeclampsia:

- Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg on two occasions at least four hours apart while the patient is on bed rest.
- Mild proteinuria (≥ 0.3 grams /day) .

Exclusion Criteria:-

1) Malnutrition.
2) Previous or gestational diabetes mellitus.
3) Renal diseases.
4) Previous significant proteinuria.
5) Super imposed preeclampsia.
6) Continuous use of calcium channel blocker.
7) Drugs that alter sodium level.
8) Major fetal malformations.
9) Intrauterine fetal death.
10) Multiple pregnancies.

Methodology:

All included women will be subjected to the following:

1- History taking with particular emphasis on past medical history and obstetrical history.
2- General, abdominal and local examination.
3- An ultrasound assessment.
4- Collected 24 hour urine to determine proteinuria is made by using an automatic analyzer **(*Cobas Inregra 400 Plus ,Roche, Basel, SWITZERLAND***) by immuneturbidimetic method .

Procedures:

1-Patients concenting to participation study will collect a random spot urine sample in a clean leak- proof plastic container.

2- Use 2ml fresh urine sample for analysis and, If transport is delayed, specimens should be kept refregirated at 2-8 °C.

3- Sodium, Calcium and Creatinine will be measured.

4-The laboratory tests will be done at the clinical pathology laboratories at the same hospital in an automated clinical chemistry analyzer ***(Beckman Coulter AU480 , USA*)**.

5- Natriuria will be measured using an ion-selective electrode and results will be expressed as mEq/L.

6- Calcuria will be measured using a dye binding method and results will be expressed as mg/dl.