www.nephropathol.com DOI: 10.15171/jnp.2017.58 J Nephropathol. 2017;6(4):356-358

Journal of Nephropathology

The level of urinary endothelin in patients with urinary reflux

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ARTICLE INFO

Article type:
Original Article

Article history:
Received: 10 March 2017
Accepted: 15 June 2017
Published online: 29 June 2017
DOI: 10.15171/jnp.2017.58

Keywords:
Reflux
Endothelin
Voiding cystourethrography
Chronic renal failure
Vesicoureteral reflux

ABSTRACT

Background: In different tissues, the endothelin is produced by vascular endothelium. They are potent vasoconstrictor peptides. There is a little information about the role of endothelin in reflux nephropathy.

Objectives: The aim of this study is to evaluate urinary levels of endothelin in patients with vesicoureteral reflux (VUR).

Patients and Methods: It was a cross-sectional study that conducted on 81 children who received voiding cystourethrogram (VCUG). Based on VCUG reports, patients were divided into two groups; with reflux (40 persons) and without reflux (41 persons). We got a urine sample from patients with mid-stream or urine bag method. The endothelin level was assessed with ELISA immunoassay. Data was analyzed using SPSS 16.

Results: Based on VCUG reports, 40 patients (49.4%) had urinary reflux, of them 20 cases suffered from unilateral urinary reflux and others from bilateral. Of 40 patients with reflux, 23 cases (57.5% of reflux group) had kidney scar and seven individuals (17.5%) had abnormal kidney sonography. Of patients with urinary reflux, 13 cases (32.5%) had grade1 urinary reflux, 8 cases (20%) grade 2, and 5 cases (12.5%) grade 3 and finally 14 cases (35%) grade 4. The UET-1 levels were significantly higher in VUR patients compared to the control group ($P<0.001$). Comparison of mean endothelin levels between two groups was done using Mann-Whitney U test and was statistically significance ($P<0.001$). We used Kruskal-Wallis for comparison of endothelin levels in different grades of reflux ($P<0.001$).

Conclusions: Urine endothelin-1 level can be considered as an alternative to VCUG for screening vesicourethral reflux.

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Implication for health policy/practice/research/medical education:
Urine endothelin-1 level can be considered as an alternative to VCUG for screening VUR. According to significant changes in the different grades of reflux, it is helpful in determining the severity of VUR. It can at least prevent performing unnecessary VCUG in low-risk patients.

Please cite this paper as: Azarfar A, Esmaeeli M, Naseri M, Badiee Aval S, Ghanee Sharbaf F, Ravanshad S, et al. The level of urinary endothelin in patients with urinary reflux. J Nephropathol. 2017;6(4):356-358. DOI: 10.15171/jnp.2017.58.

1. Introduction

Vesicoureteral reflux (VUR) exists in one third of children with febrile urinary tract infection, and has been connected with an increased risk of renal scarring (1). Renal injury associated with VUR creates renal infections in children or renal mal-development during fetal life and may cause hypertension and chronic renal failure. Early diagnosis and rapid medical or surgical treatment are advised to prevent renal damage. In the past, voiding uretrocystogram was used for diagnosis of all children with urinary tract infections who received long-term antibiotic

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prophylaxis or surgery. Nowadays, several trials have suggested to improve diagnostic and surgical procedures in children suffering from VUR (2). Endothelin is produced by vascular endothelium in different tissues. They are potent vasoconstrictor peptides. There is a little information about the role of the endothelin in reflux nephropathy (3).

2. Objectives

The aim of this study is to evaluate urinary level of endothelin in patients with VUR.

3. Patients and Methods

It is a cross-sectional study was conducted on 81 children aged 5 to 48 months. The team medical had asked them for performing voiding cystourethrogram (VCUG) and were referred to the radiology department. Based on VCUG reports, patients were divided into two groups; with reflux (40 person) and without reflux (41 person). A urine sample with mid-stream or urine bag method was obtained and was sent to laboratory to detect urine biomarkers. To test, urine samples were centrifuged then urine supernatant were kept in -20°C. Endothelin serum value was assessed with ELISA immunoassay.

3.1. Ethical issues

The research followed the tenets of the Declaration of Helsinki. The research was approved by the ethical committee of Mashhad University of Medical Sciences (Ethical code #ir.mums.rec.1391.705)

3.2. Statistical analysis

Data was analyzed using SPSS 16. We compared endothelin levels between two groups (with and without reflux). We used Kruskal-Wallis for comparison of endothelin level in different grades of reflux and Mann-Whitney U test for pairwise comparisons. We evaluated the correlations with Spearman's test. In this study, we consider $P<0.05$ to be meaningful.

4. Results

In this study, 81 patients were enrolled, of them, 31 patients (38.3%) were male. The VCUG reports revealed that 40 patients (49.4%) had urinary reflux of them 20 cases (50%) suffered from unilateral urinary reflux and others bilateral. Of 40 patients with reflux, 23 cases (57.5%) had kidney scars and 7 persons (17.5%) had abnormal kidney sonography too. In patients with urinary reflux, 13 cases (32.5%) had grade1 urinary reflux, 8 cases (20%) grade 2, 5 cases (12.5%) grade 3 and 14 cases (35%) grade 4. Mean endothelin level in two groups is shown in Table 1.

Comparison of mean endothelin levels between two groups was done using Mann-Whitney U test. The mean difference between two groups was statistically significance ($P<0.001$). Table 2 shows endothelin levels in different grades of reflux.

We used Kruskal-Wallis for comparison of endothelin level in different grades of reflux. It was statistically significant ($P<0.001$). We used Mann-Whitney U test for pairwise comparisons. Table 3 shows the results.

We evaluated the correlation between endothelin levels and age and gender of patients with reflux, using Spearman's test; it was not statistically significant ($P>0.05$).

5. Discussion

This study showed that endothelin level in patient with reflux was more than the without reflux group. Study of different grades of urinary reflux revealed that endothelin level in grade 4 was significantly higher than other grades, grade 3 was significantly higher than grade 2, but grade 2 was not comparable with grade 1. In reflux group, there was no correlation between endothelin levels and age and gender.

Two research works stated that urinary endothelin-1 excretion in patients with primary VUR was significantly higher than normal, and it increased in proportion to the grade of reflux (4,5). However, based on dimercaptosuccinic acid (DMSA) uptake,

Table 1. Endothelin level (ρg/mL) in reflux and without reflux groups

Groups	Minimum	Maximum	Mean	SD
With reflux	0.01	100	7.2728	22.1159
Without reflux	0.01	0.02	0.0107	0.00264

Table 2. Endothelin level (ρg/mL) in different grades of reflux

Grades of reflux	Minimum	Maximum	Mean	SD
1	0.01	0.9	0.4777	0.355
2	0.2	1.30	0.7625	0.403
3	1.40	2.80	1.9	0.557
4	1.50	100	19.22	35.07

Table 3. Pairwise comparisons of endothelin level in different grades of reflux

Grades of reflux	1	2	3
2	*P*=0.104		*P*=0.002
3	*P*<0.001	*P*=0.002	
4	*P*<0.001	*P*<0.001	*P*=0.005

they did not find any relationship between endothelin level and renal parenchymal and function damage (4, 5). Additionally in graft injury, early urinary biomarkers were a useful means. A recent study, showed more accuracy of urinary endothelin-1 to predict the severity of ischemic injury than other markers (6). A more recent study conducted on urinary endothelin-1 excretion, based on morpho-functional damage lateralization in reflux nephropathy, detected the increase of urinary endothelin-1 excretion in reflux nephropathy, especially when renal functional injury was lateralized (3). Likewise, a study researched in children with urinary tract infections used urine endothelin-1 levels as a predictor of renal scarring (7). They concluded that, children with normal renal function, urine endothelin-1 can be applied for prediction of renal scarring. They suggested avoiding unnecessary DMSA studies while, measuring urine levels of endothelin-1 can be helpful (7). Furthermore another study in 2011, detected that injection of endothelin in diabetic hypertensive mouse could cause significant decrease in renal blood flow, decrease of the blood supply to the cortex and medulla of kidney, and could cause vasoconstriction in the medulla (8).

6. Conclusions

Urine endothelin-1 level can be considered as an alternative to VCUG for screening VUR. Also, due to significant changes in the different grades of reflux, it is helpful in determining the severity of VUR. It can at least prevent performing unnecessary VCUG in low-risk patients.

Limitations of our study

One of the important limitations of our study was the low sample size, therefore we suggest a more extensive study with follow up of patients.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Authors' contribution

AA, YR, ME, MN and SR provided technical assistance, collection and preparation of the manuscript. YR analysis of the data. YR, HMM, SBA and FG designed, supervised the study and prepared the final draft of the article.

Funding/Support

This study was supported by Mashhad University of Medical Sciences (Grant #910535 as a M.D thesis of Sara Molkara).

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