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Prevalence of Microalbuminuria and Its Association with Severe Urinary Reflux and Renal Scarring with Reflux Nephropathy in Children Aged Less Than 12 Years in Ilam, Iran

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Abstract

Background: Vesicoureteral reflux is a common urinary tract abnormality, which could damage the renal parenchyma. The present study aimed to investigate the prevalence of microalbuminuria and its association with the severity of urinary reflux and renal scarring with reflux nephropathy in children aged less than 12 years referred to Imam Khomeini Hospital in Ilam, Iran.
Methods: This longitudinal study was conducted during one year on the hospitalized patients who had tested positive for urine and urine culture. After the treatment of urinary tract infection and obtaining a negative urine culture, isotope cystography or radiographic cystography was performed to diagnose urinary reflux. Data analysis was performed in SPSS version 20 using descriptive statistics, chi-square, and correlation-coefficients.
Results: The prevalence of microalbuminuria in Ilam province was 35.7%. No significant difference was observed between the rates of microalbuminuria and reflux ($P > 0.05$). However, the inverse correlation in this regard was not considered significant ($P > 0.05$). A direct correlation was observed between the rate of microalbuminuria and the incidence and severity of scars, which was considered significant ($P < 0.05$).
Conclusions: According to the results, the mean rate of microalbuminuria in reflux decreased with the increased degree of reflux. Due to the changes in microalbuminuria compared to the severity of urinary reflux, this method cannot be used to determine the severity of reflux, which it could be considered an influential factor and a method used for the early diagnosis and follow-up of patients and preventing final kidney damage and renal failure.

Keywords: Microalbuminuria, Urinary Reflux, Scar, Children, Ilam

1. Background

Vesicoureteral reflux is the backward flow of urine from the bladder to the ureter and into the kidneys (1), which increases susceptibility to urinary tract infections, renal scarring, hypertension, and chronic renal failure (2, 3). Reflux nephropathy causes renal failure in 25% of the children undergoing dialysis and 10 - 15% of the adults waiting for a kidney transplant (4). In a study, Kwak reported that the rate of albuminuria in children with vesicoureteral reflux and urinary tract infections was significantly higher compared to the children in the control group (5). Furthermore, Lahdes-Vasama stated that proteinuria was the most significant predictor of poor prognosis in the adults who had reflux in childhood (6). The study by Silva et al. also indicated that a higher percentage of male patients had moderate-to-severe reflux, and the difference in this regard was significant. In the mentioned study, the incidence of renal scarring was similar between the two genders although it was not statistically significant (7). In the study by Basic et al., the amount of albumin secreted in the group with reflux was significantly higher compared to the group without reflux (8).

As a general principle, most studies have shown higher urinary protein secretion in patients with reflux compared to healthy individuals (9). The occurrence of microalbuminuria may indicate the onset of parenchymal kidney damage (10). In the study by Bell, albumin secretion increased with the increased severity of scarring and reflux.

In addition, a positive, significant correlation was reported between the degree of reflux and the amount of microalbuminuria in the mentioned study (11). According to Jung and Koo, 24-hour urinary microalbumin secretion was significantly higher in the group with scarring and reflux compared to the group without scarring and reflux, while no correlation was observed between the severity of reflux and the amount of urinary microalbumin (12). In the study by Ginevri, microalbuminuria was elevated in 82 patients with vesicoureteral reflux in all the cases, which was associated with the severity of reflux and the degree of renal function (13). On the other hand, Mortazavi and Zakeri reported no significant correlation between the degree of reflux and the amount of microalbuminuria in 87 children with vesicoureteral reflux (13).

2. Objectives

Today, microalbuminuria is considered a risk factor for nephropathy in the adult population, while few studies have investigated children. The present study aimed to investigate the changes in microalbuminuria and its association with the severity of urinary reflux and renal scarring in children with reflux nephropathy.

3. Methods

This longitudinal study was conducted during one year on the children aged less than 12 years with vesicoureteral reflux who were referred to the pediatric educational center of Imam Khomeini Hospital in Ilam during 2017 - 2018. Preliminary data were obtained on age, gender, height, weight, blood pressure, degree of reflux, urea, creatinine, creatinine clearance, and urinary microalbumin from the patients' records and recorded in data collection forms.

Isotope cystography (DRNC) or radiographic cystography (VCUG) was performed on the hospitalized patients who tested positive for urine and urine culture after the treatment of urinary tract infection, and the patients were visited by a nephrologist. Diagnosis of urinary reflux was based on the VCUG and DRNC scans. Random urea, creatinine, and microalbumin tests were also requested. The albumin-to-creatinine ratio in random urine within the range of 0.3 - 0.03 (30 - 300 mg in 24 hours) was considered as microalbuminuria. In addition, DMSA scans were requested in the children with reflux to examine kidney scarring, urea, creatinine, and random urinary microalbumin after 4 - 6 weeks.

Data analysis was performed in SPSS version 20 using descriptive statistics, and chi-square was also applied to compare the qualitative findings. Moreover, Pearson's and Spearman's correlation-coefficients were used to determine the correlations between the variables.

4. Results

Out of 90 patients, 61 were female (67.8%), and 29 were male (32.2%). The children were within the age range of one month to 12 years, while 55 cases (61.1%) were aged 1 - 3 years, 18 (20%) were aged 4 - 6 years, 10 (11.1%) were aged 7-9 years, and seven cases (7.8%) were aged 10 - 12 years. The mean age of the children was 41.21 $\pm$ 37.71 years (Table 1).

Table 1. Descriptive Statistics of Research Variables

Variables	Mean $\pm$ SD
Age (y)	37.71 $\pm$ 41.21
Height (cm)	86.27 $\pm$ 26.16
Body mass index (kg/m^2)	13.08 $\pm$ 9.06

Among 90 patients, 28 cases (31.1%) had mild reflux (grades I and II), of which nine cases (32.1%) had right renal reflux, 14 cases (50%) had left renal reflux, and five cases (17.8%) had bilateral reflux. In addition, 34 patients (37.8%) had moderate reflux (grade III), of which seven cases (20.5%) had right kidney reflux, 14 cases (41.1%) had left kidney reflux, and 13 cases (38.2%) had bilateral reflux. Also, 28 patients (31.1%) had severe reflux (grades IV and V), three patients (10.7%) had right kidney reflux, 10 patients (35.7%) had left kidney reflux, and 15 patients (53.5%) had bilateral reflux.

The rate of microalbuminuria and pyelonephritis changes was higher in the male patients compared to the females. In both genders, the rate of microalbuminuria was above normal in the presence of pyelonephritis. However, no significant correlation was observed in this regard. In the female patients, microalbuminuria was highest in the right scar. Furthermore, the obtained results indicated that 57.1% of the male patients had pyelonephritis with severe reflux, while no significant correlation was observed between the male and female patients in terms of reflux and the incidence of scarring. Moderate reflux was also observed, as well as a significant correlation between the degree of reflux and the incidence of scarring in the male and female patients.

The correlation-coefficient results indicated direct correlations between microalbuminuria, age, height, creatinine, and blood pressure, as well as between microalbuminuria and the glomerular filtration rate (GFR) and DMSA, which was not considered significant ($P > 0.05$). In addition, the correlation-coefficient results demonstrated

a direct and significant correlation between microalbuminuria and the presence of reflux ($P < 0.05$) (Table 2).

The results of linear multivariate regression analysis to determine the effects of age, height, blood pressure, GFR, and degree of reflux on the rate of microalbuminuria indicated that the degree of reflux had the most significant effect in this regard ($\beta = 0.24$). Notably, the other variables were eliminated from the model since they were not significant (Table 3).

The results of Spearman's correlation-coefficient indicated an inverse and significant correlation between the degree of urinary reflux and age ($P < 0.05$), as well as a direct and significant correlation between the coefficient of scarring incidence and age ($P < 0.05$). Despite unilateral reflux, the rate of microalbuminuria was higher in the male patients compared to the females, while in bilateral reflux, the rate of microalbuminuria was higher in the females compared to the males. A significant correlation was also observed between microalbuminuria and the presence of reflux in the female patients ($P < 0.05$) (Table 4).

5. Discussion

The present study was conducted on 90 patients with vesicoureteral reflux to evaluate the prevalence of microalbuminuria and its association with the degree of reflux and renal scarring. According to the obtained results, the variables of age, height, creatinine, GFR, and scarring rate had no significant effects on albuminuria; this is consistent with the results obtained by Silva et al. (7). In the present study, a significant correlation was observed between age and the presence of urinary reflux. This correlation was also significant between microalbuminuria and the presence of reflux in the female patients. With the increased degree of reflux, microalbuminuria significantly increased.

Despite unilateral reflux, the rate of microalbuminuria was higher in the male patients compared to the females. In bilateral reflux, the rate of microalbuminuria was higher in the female patients compared to the males, and a significant correlation was observed between microalbuminuria and the presence of reflux in the female patients. This finding is consistent with the study by Bell et al. (11), which indicated a positive and significant correlation between the degree of reflux and the rate of microalbuminuria. In the study by Jung and Koo, no association was reported between the degree of reflux and the rate of microalbuminuria, which is also consistent with the current research (12). Despite some differences, there seems to be a direct correlation between the presence of reflux and the occurrence of microalbuminuria. The insignificance of the correlation between the rate of microalbuminuria and the degree of reflux could be due to differences in the treatment and follow-up of patients with varying degrees of reflux.

The findings of the current research demonstrated a direct and significant correlation between the degree of reflux and the incidence of scarring with age ($P < 0.05$). Male patients are commonly diagnosed with fetal hydronephrosis, while females are often diagnosed with urinary tract infections. Therefore, disease severity seems to be higher in males.

In the present study, microalbuminuria and scarring were more prevalent in the male patients compared to the females. In both genders, the rate of microalbuminuria was above the normal range in pyelonephritis. However, no significant correlation was observed in this regard. The rate of microalbuminuria was also highest in the female patients in the right scar. In the study by Basic et al., microalbuminuria was reported to be more prevalent in the group with reflux and scarring compared to the control group (8). In the study by Jung and Koo, the rate of microalbuminuria was significantly higher in the group with reflux and renal scarring compared to the group without reflux and renal scarring, while no correlation was reported between the severity of microalbuminuria and reflux (12).

In the present study, a direct correlation was observed between the correlation-coefficient of the degree of urinary reflux and gender, as well as an inverse correlation with the incidence of scars, while the correlation was not considered significant. In the study conducted by Kwak et al., the rate of microalbuminuria was significantly higher in children with vesicoureteral reflux and urinary tract infections compared to the control group (5). In another research, Julia claimed that the ratio of microalbumin to urinary creatinine could be a prognostic marker of renal function in children with urinary tract infections and vesicoureteral reflux (14). In the study by Benaired regarding renal function in adults with reflux in childhood, proteinuria was reported to be the most significant predictor of poor prognosis (15). On the other hand, Coco and Jacobs reported that the study groups had no significant difference in terms of microalbuminuria (16).

5.1. Conclusions

Due to changes in microalbuminuria compared to the severity of urinary reflux, this method cannot be used to determine the severity of reflux, while it is effective as a determinant of the prognosis of reflux and could be used for patient follow-up and to prevent final damage and kidney scars.

Table 2. Correlations Between Age, Height, Creatinine, Urinary Reflux, Renal Scarring, and Degree of Urinary Reflux with Microalbuminuria

	Age	Height	Creatinine	GFR	DMSA	DP	VCUG
r	-0.07	-0.1	-0.04	0.08	0.1	-0.12	0.43
P-value	0.49 [a]	0.33 [a]	0.64 [a]	0.45 [a]	0.31 [b]	0.23 [a]	0.000 [b]

[a] Pearson's correlation-coefficient
[b] Spearman's correlation-coefficient

Table 3. Effect of Degree of Reflux on Microalbuminuria Rate

	B	Std. Error	Beta	*t*	P-Value
Degree of reflux	0.24	0.06	0.33	3.12	0.002

Table 4. Correlation of Urinary Reflux, Renal Scarring, and Degree of Urinary Reflux with Age

	DMSA	VCUG
r [a]	0.23	-0.214
P-value	0.02	0.04

[a] Spearman's correlation-coefficient

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Footnotes

Authors' Contribution: KM.M, MN developed and designed the evaluation, collected the clinical data (TF) and drafted the manuscript. KM.M, Sh.E and MJ participated in the study conception and design, supervised the study and revised the manuscript critically for important intellectual contents. Sh.E revised the manuscript critically for important intellectual contents. All authors read and approved the final manuscript.

Conflict of Interests: The authors declared no conflict of interest.

Data Reproducibility: The datasets used and/or analyzed in the current study are attained from the corresponding author on reasonable request.

Ethical Approval: The required permit to conduct this research was obtained from the Vice Chancellor for Research of Ilam University of Medical Sciences, Iran (ethics code: IR.MEDILAM.REC.1399.100). All ethical principles were observed in this study. The participants were informed of the research objectives and implementation stages and were also assured of confidentiality terms regarding their information. Link: ethics.research.ac.ir/EthicsProposalView.php?id=138458.

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