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# Urinary Beta 2-Microglobulin as a Prognostic Marker in Children With Pyelonephritis

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ABSTRACT

***Background:*** Urinary tract infection (UTI) is common in children. UTI with or without vesico-ureteral reflux (VUR) may result in renal scarring. Severe renal scarring impairs renal function and may result in hypertension, renal insufficiency, and end stage renal disease requiring dialyses or transplantation. Beta 2 micro-globulin (β2MG) is a low molecular weight protein freely filtered by the glomeruli and then actively reabsorbed normally up to 99.9% in the proximal tubules; its urinary excretion is an indication of proximal tubular cell dysfunction.

***Objectives:*** The current study aimed to determine whether urinary β2MG excretion would be elevated in patients with various grades of renal scar, and also its relationship with renal outcome in long term follow-up.

***Materials and Methods:*** Urinary β2MG and Creatinine (Cr) were measured in 83 spot urine samples of patients that 53 of them did DMSA renal scan both at the time of admission to confirm pyelonephritis, and 6 month later to detect scars. β2MG was measured by radioimmunoassay method using β2MG 96-test kit (RADIM Company; Germany), and the creatinine was measurd by spectrophotometry and was recorded as microgram per mg creatinine. Twenty children had various grades of renal scars. Results were compared with the ratios of 19 children with low uptake scanning, 14 children with normal scanning after recovery from pyelonephritis, and 30 normal children served as controls. EXCEL and SPSS softwares were employed to compare the mean urinary ß2MG in groups by student t-test, ANOVA, and Unpaired t-test at *P*,0.05 significance level. Subsequently patients were followed up for 6 years.

***Results:*** The mean urinary β2MG/Cr ratio was significantly higher in the scarring group (5.23 ±10.6) than in the normal group (0.19 ± 0.2), and in low uptake group (0.49 ± 0.86) ($P < 0.05$). When mean β2MG/Cr ratios were compared for each grade of scarring; patients with sever scar (grade III) had higher values (14.69 ± 15.82) than grades I (0.36 ± 0.35) and II (3.37 ± 5.20) ($P < 0.05$). Patients without renal scar had a β2MG/Cr ratio below 0.46 microgram/mg Cr. The mean β2MG was also higher in the refluxing group (3.45 ± 7.97) than nonrefluxing group (0.23 ± 0.24) ug/mgCr ($P = 0.01$). Three patients who had the highest β2MG/Cr ratio values (33.3, 27, and 26.6 microgram/mg Cr) had sever scar that rapidly progressed to ESRD. They were transplanted 2 years later; after transplantation they still had recurrent UTIs. 2nd patient underwent native nephrectomy for renal abscess.

***Conclusions:*** Results of the current study revealed that mean β2MG/Cr ratio was higher in patients with renal scar and poor outcome. Measurement of Urinary β2MG may be useful in the early detection of tubular damage in refluxing patients and patients with renal scars and has prognostic significance.



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*Implication for health policy/practice/research/medical education:*
Urinary tract infection (UTI) is common in children. The current study aimed to determine whether urinary B2MG excretion would be elevated in patients with various grades of renal scar.

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## 1. Background

Urinary tract infection (UTI) is one of the most common infectious diseases in children (1). The risk of UTI in children is up to 5% in girls and 1.6% in boys (2). Girls have a 30% recurrence within the first year and 50% within 5 years after the first UTI (2). Vesico-ureteral reflux (VUR), reflux of urine from bladder to ureters is considered as a risk factor for pyelonephritis. VUR is present in 1.8% of all children while its prevalence in children with UTI is as high as 34% (1). Sixteen to forty percent of the siblings of these children have VUR as well. It has been shown that VUR is inherited in an autosomal dominant pattern (2). UTI is the most common clue to VUR diagnosis. Since the combination of VUR and UTI leads to renal damage, and subsequenthypertension, renal insufficiency, and end stage renal disease requiring dialyses or transplantation, diagnosis of VUR in patients presenting with UTI is of great importance (1).

Voiding Cysto-Uretero-Graphy (VCUG) is carried out in children presenting with pyelonephritis and recurrent UTI to rule out VUR (3).

Dimercaptosuccinic acid scan (DMSA), which is commonly used to detect renal damages after pyelonephritis, has a great burden of radiation exposure. Thus, it is of utmost importance to find out a method to detect VUR and renal scars without the above-mentioned disadvantages.

There have been several efforts to diagnose VUR and renal injuries without radiation and catheterization, and to evaluate prognosis in these children. In a study entitled" Clinical significance of urinary interleukin -6 in children with Reflux Nephropathy (RN), Wang J *et al.* concluded that urinary interleukin 6 may be useful in monitoring progression of reflux nephropathy (4). A non-invasive test for VUR in children was introduced by Mevorach RA in the year 2000; he processed acoustic signals during urination and detected VUR in 35/37 of patients in VUR group and no VUR in 16 out of 17 non-refluxing children (5).

β2MG is a low molecular weight protein of HLA complex, which is freely filtered via glomerular membrane and nearly 99.9% is reabsorbed in proximal tubules. It has been introduced as an indicator of proximal tubular dysfunction (1).

β2MG is measured by enzyme linked immunosorbent assay (ELISA) or radioimmunoassay. Since it is a nonspecific index of tubular damage, it can not differentiate different pathologies of urinary system, however it can be used to verify and follow up known cases. Sensitivity and specificity of this method in diagnosing renal scar is not investigated yet.

Evaluation of renal function in children with primary VUR was undertaken by Ohta S *et al.* in 1990, it was found that β2MG, Alpha1 micro-globulin, N-acetyl-B-D-Glucosaminidase (NAG) were elevated in 76%, 51% and 92% of patients respectively (6).

β2 Microglobulinuria in children with VUR and recurrent UTI was found to be abnormal in urine and serum of these patients by Kaminska *et al.* in 2000 (7). In a study entitled Urinary β2 Micro globulin as a marker for VUR, Dr Asadi F K found that urinary β2MG was increased in high grade VUR (8).

## 2. Objectives

The current study aimed to mesure the urinary levels of β2MG and creatinine in children who were to undergo VCUG and DMSA scan in Mofid Children's Hospital and to evaluate its relationship with VUR and renal scars and its grades; then to follow up these patients for 6 years.

## 3. Materials and Methods

All patients less than 12 years admitted for pyelonephritis in Mofid Children Hospital from December 2005 to December 2006 were included in the study.Patients with renal failure or on nephrotoxic drugs were excluded. β2MG and Creatinine were measured in 83 urine samples (47 sample from patients with VUR and 36 from non refluxing children) at the time of VCUG using 96 test β2MG kit (Radim Co. Germany).

β2MG was measured by enzyme immunoassay (EIA) method and Cr with Auto analyzer. Standard VCUG was performed using contrast medium and was reported by a radiologist based on international VUR classification. The urine samples were obtained during the catheterization phase of VCUG and were neutralized with 0.1% sodium hydroxide if pH < 6 and stored at 20 degrees centigrade until tested.

β2MG/Cr ratio was calculated to consider diuresis dependent excretion of this protein. VCUG and urine sample analysis were performed in Mofid Children Hospital and the operators were not aware of the results of the

| **Box.** Scar Classification Based on Dimercaptosuccinic acid (DMSA) Scan |
|---|
| Type 1: No more than two scarred areas |
| Type 2: More than two scars with some area of normal parenchyma between them |
| Type 3: Generalized damage to the whole kidney similar to obstructive nephropathy (i.e.' contraction of the whole kidney without or with very few scars in the outline) |
| Type 4: End stage "shrunken" kidney with little or no uptake of DMSA, (i.e., less than 10% of the overall function). |

other test. DMSA renal scan was performed in 43 patients with pyelonephritis at the time of infection and 6 month later to detect scar, and was classified in 4 grades as proposed by Goldraich *et al.* (9) (*Box.*).

Urinary β2MG and Cr were measured in random urine samples in 83 cases, and 20 children with various grades of scar. The results were compared with ratios of 19 children with low uptake scanning, 14 normal scanning, and 30 normal healthy children. The goal and procedure of the study were fully explained to the families of the cases and considering the ease and time sparing nature of the procedure, their cooperation was excellent.

β2MG/Cr ± SD was calculated and recorded in cases under study and the control group with different grades of VUR and renal scars. Excel and SPSS softwares were employed to compare the mean β2MG/Cr ratio in the control group and those of patients with different VUR and renal scar grades by student t-test, ANOVA, and Unpaired t-test samples assuming unequal variances.

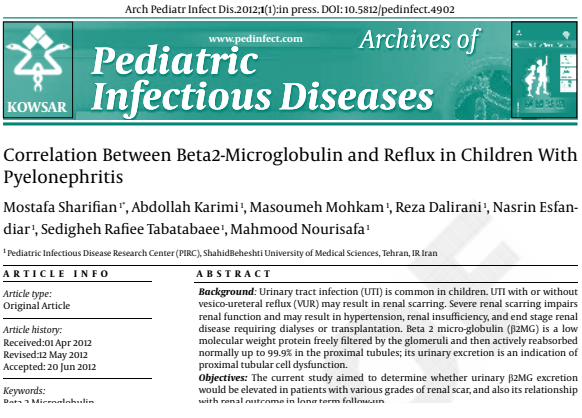
## 4. Results

Of the 83 children under study, there were 47 cases (31 girls and 16 boys) with VUR and 36 cases without VUR (24 girls and 12 boys). Twenty one patients (13 girls and 8 boys) had bilateral VUR while unilateral VUR was seen in the remaining 26 patients (18 girls and 8 boys). The mean β2MG/Cr ratio was higher in patients with VUR grades 4 and 5 (8.93 ± 12.01) than those of patients with VUR grades 1 to 3 (0.81 ± 3.04) ($P = 0.02$). Maximum β2MG/Cr ratio was detected in patients with grade 4 VUR (33.3) and the minimum was zero in non-refluxing patients.

The mean urinary β2MG/Cr ratios were 5.23 ± 10.6 in the scarring group , 0.19 ± 0.2 in the normal group ,and 0.49 ± 0.86 in the low uptake group respectively ($P < 0.05$). When mean β2MG/Cr ratios were compared for each grade of scarring; patients with grade III had higher values (14.69 ± 15.82) than grades 1 (0.36 ± 0.35) and 2 (3.37 ± 5.2) patients ($P = 0.02$). Patients without renal scar had β2MG/Cr ratio below 0.46-microgram/mg. Mean β2MG/Cr ratio was 3.55 and 8.41 in patients with unilateral and bilateral scar respectively ($P > 0.05$).

Forty one percent of patients with VUR and 25% of patients without VUR had renal scars ($P > 0.05$). The mean β2MG/Cr ratio was higher in the refluxing patients (3/45 ± 7.97) than non-refluxing group (0.23 ± 0.24) ug/mgCr ($P = 0.01$). No significant difference was found in β2MG/Cr ratio values in patients with VUR grades 1, 2 and 3 and non refluxing patients (0.20 ± 0.7, 1.21 ± 3.98, 0.21 ± 0.18 and 0.23 ± 0.24 respectively ($P = 0.29$).

No patient in the non-refluxing group had β2MG /Cr ratio higher than 0.85. There was no significant difference in β2MG/Cr ratios in patients with bilateral (4.94 ± 9.91) and unilateral (1.91 ± 5.9) reflux ($P = 0.11$). Three patients with high grade VUR and the highest levels of β2MG/Cr ratio (33.3, 27 and 26.6) progressed to renal failure very rapidly and in 2 years time the first patient was treated by hemodialysis and the second and third patients underwent pre-emptive renal transplantation (*Figure 1*). The first patient also subsequently underwent renal transplantation. After 6 years his plasma creatinine was around 1.7 mg/dL. He had repeated episodes of UTI which was treated as outpatient. After transplantation, the second patient also had repeated episodes of UTI and rising Cr so that she was treated parenterally as inpatient bases. She underwent left side native nephrectomy because of persistent UTI and xanthogranulomatous pyelonephritis. Her last Cr was around 4- 5 mg/dL waiting for her second transplant.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Correlation Between Beta2-Microglobulin and Reflux in Children With Pyelonephritis

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***Background:*** Urinary tract infection (UTI) is common in children. UTI with or without vesico-ureteral reflux (VUR) may result in renal scarring. Severe renal scarring impairs renal function and may result in hypertension, renal insufficiency, and end stage renal disease requiring dialyses or transplantation. Beta 2 micro-globulin (β2MG) is a low molecular weight protein freely filtered by the glomeruli and then actively reabsorbed normally up to 99.9% in the proximal tubules; its urinary excretion is an indication of proximal tubular cell dysfunction.

***Objectives:*** The current study aimed to determine whether urinary β2MG excretion would be elevated in patients with various grades of renal scar, and also its relationship

**Figure 1.** Mean urinary Beta 2-Microglobulin in Relation to Grades of Renal Scars and Outcome in Children With Pyelonephritis

## 5. Discussion

Vesico-ureteral reflux is present in 1.8% of children and has been long known as a leading risk factor for UTI and renal scar in children. Evaluation for VUR is essential in children with UTI (1, 6, 7).

VUR tends to be more common at lower ages. It is diagnosed in 70% of infants with UTI while this probability decreases to 25% in children under 4, 15% in children under

12, and 5% in adults (1).

Dimercaptosuccinic Acid Scan (DMSA) reveals that one third of the children with VUR have scars in their kidneys and reflux nephropathy accounts for up to 25% of pediatric cases of end stage renal disease (ESDR) (8, 10). Even isotope VCUG, which is used to follow up the patients and to screen their siblings, is associated with exposure to a remarkable radiation. Recently, there have been tremendous efforts to establish a diagnostic module for VUR and renal scar without radiation (8, 10-12).

Measurement of urinary level of β2MG is one of these noninvasive modules. Ohta S. studied 62 under 2 year-old children with VUR for urinary level of β2MG, α1-microglubolin and N-acetyl-β-D-glucosaminidase (NAG); 45% of the cases had VUR grades 4 and 5. Urinary levels of β2MG, α1-microglubolin and N-acetyl-β-D-glucosaminidase were increased in 76%, 51% and 92% of these cases respectively (6).

Asadi FK in a study in 1996 showed that urinary β2MG was higher in patients with VUR than the patients without VUR (8). The study included 56 cases of VUR of different grades and 39 children in control group. The mean β2MG/Cr ratio was higher in the cases with VUR, and thecut off point for VUR was accounted as 0.72 μg/mgCr. This value was based on the fact that all cases without VUR had a β2MG/Cr ratio of below this value. Comparing this ratio with those of patients with different grades of VUR and the patients without VUR in the current study, revealed that β2MG/Cr ratio was significantly higher in patients with VUR. This increase was more remarkable in patients with VUR of grades 4 and 5 (8.93 *vs.* 0.23). This ratio was significantly higher in children with renal scar as well. Another study on 204 patients has revealed that β2MG/Cr ratio increased in 36% of the cases and remarkably decreased after corrective surgery of VUR (10).Another study investigated β2MG/Cr ratio as an indicator of tubular damage in 82 patients with VUR. β2MG/ Cr ratio increased in all of them (11).

The point in the current study and Asadi's study was lack of significance of the difference between the β2MG/Cr ratios of patients with VUR grades 1-3 and those of patients without VUR. It suggests that β2MG/Cr ratio cannot be a good indicator in patients of lower grades of VUR who do not have remarkable tubular damage. On the other hand, in patients with higher grades of VUR and more tubular damage, measurement of urinary level of β2MG can be used as a reliable screening test.

VUR grades 1-3 are most likely self limited (70-80%) and can be managed successfully by prophylactic antibiotic therapy and/or prompt follow-up and rarely need a corrective surgery; however, VUR of higher grades is self limited in 10 to 40% of the cases and mostly warrants anti-reflux surgery. Thus, it can be claimed that measuring urinary level of β2MG is an effective module in diagnosing the patients who need a surgery (1-3). Measurement of β2MG may be useful in the early detection of tubular damage in refluxing patients and patients with renal scars.

In the current study standard deviation was high; this was prominent in analysis of patients with VUR, this could be the result of the low number of patients and the fact that scar can occur in Pyelonephritis without reflux. Further studies are required with a higher number of patients.

This study revealed that the maximum β2MG/Cr ratio value in non refluxing children and those without renal scar was 0.85 and 0.46 microgram/mg Cr respectively, higher values can be considered as a cut off point in screening children for high grade VUR and renal scar.

Measurement of urinary level of β2MG is recommended prior to VCUG in patients with UTI and the siblings of the patients with VUR. Urinary β2MG/Cr ratio Values can be used to evaluate the prognosis in patients with VUR and renal scars.

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## Authors' Contribution

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