Original Article

Association of urinary transforming growth factor-β1 with the ureteropelvic junction obstruction

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Abstract

Background: We aimed to compare the level of urinary transforming growth factor-beta 1 (TGF-β_1) in children with ureteropelvic junction obstruction (UPJO) with the normal peers.

Materials and Methods: In this case-control study, we enrolled children with UPJO and matched normal peers. Sterile urine was collected from the subjects and urinary TGF-β_1 was measured by ELISA method. Also, degree of the UPJO and the magnitude of the renal injury were assessed by ultrasonography and measuring glomerular filtration rate (GFR), respectively. Study variables were then compared between the study groups regarding the level of urinary TGF-β_1.

Results: A total of 25 children with UPJO (age = 7.4 ± 4.5 years; male = 16) were compared with 25 healthy peers (age = 6.8 ± 5.6 years; male = 16). Mean GFR in the UPJO and the control group were 112.4 ± 10.1 and 123.29 ± 4.4, respectively. Mean urinary TGF-β_1 in the UPJO group was 87.1 ± 12.6 pg/ml *vs* 30.5 ± 14.5 pg/ml in the control group. The level of urinary TGF-β_1 was significantly associated with the degree of TGF-β_1 and patients with grade IV hydronephrosis had the highest level of urinary TGF-β ($P = 0.0001$).

Conclusion: Based on our findings, biomarkers such as TGF-β_1 can successfully be used for confirming UPJO. However, further studies are needed to determine the proper cut point for diagnosis confirmation.

Key Words: Biomarkers, glomerular filtration rate, TGF-β_1, ureteropelvic junction obstruction

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INTRODUCTION

Ureteropelvic junction obstruction (UPJO) is the most frequent cause of hydronephrosis in children.[1-3] Diagnosis of hydronephrosis prior to further permanent injury to kidneys is crucial in such children. However, current diagnostic methods have various defects and not absolutely optimal.[3] These measures include fetal or neonatal ultrasonography, retrograde pyelogram, or diethylenetriaminepentaacetic acid (DTPA) renal scan, which all are operator dependent and may not be sensitive enough.

Upper urinary tract responds to obstruction by the activation of a cascade of molecular events and histological changes. This results in the activation of rennin-angiotensin-aldosterone system and rise of Transforming Growth Factor-beta1 (TGF-β_1).[4-6] TGF-β_1 is a biomarker produced by inflammatory

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cells and fibroblasts in different tissues. This factor has an important role in fetal development, cell differentiation, hormone secretion, and immune system.[6] TGF-β_1 is the major modulator of repair following tissue injury. Secretion of this cytokine is normally prohibited by feedback mechanisms after the completion of healing. However, TGF-β_1 release is disturbed in the course of inflammation, components of extracellular matrix accumulate and fibrosis occur.[7-12] On the other hand, overproduction of TGF-β_1Urinary TGF-β_1 can be measured in normal individuals as well as pathologic conditions of the urinary system such as vesicoureteral reflux (VUR) and hydronephrosis.[2] Measurement of biomarkers such as TGF-β_1 can help to identify the severity of congenital obstructive uropathy as well as differentiating dilated kidneys from non-dilated ones, which is beneficial in selecting the proper treatment modality (either surgical or conservative).

Due to noninvasive and sensitive characteristic of TGF-β_1, it can be easily administered for confirming the diagnosis of UPJO. However, available data are still inconsistent. This study aims to identify the predictive value of TGF-β_1 in children with UPJO by comparing the level of urinary TGF-β_1 in the affected children and the healthy peers.

MATERIALS AND METHODS

In this case-control study, 25 children with initial diagnosis of UPJO were randomly selected from patients who presented to pediatric nephrology clinic of Alzahra Hospital, Isfahan, Iran. Inclusion criteria were age ≤12 years, sterile urine analysis, and one-sided UPJO. Exclusion criteria included renal failure, posterior urethral valve, single kidney, VUR, and bilateral UPJO. The control group was selected from children who came for the vaccination in our clinic, matched for age and sex with the case group. After giving full description of the study protocol, an informed consent was obtained from the parents of the enrolled children.

In the first step, an ultrasonography from the urinary tract was performed from all participants. Ultrasonography was performed by an operator using a Sonocare ultrasonography machine. Individuals who did not meet the study criteria were then replaced with new subjects. Hydronephrosis and UPJO were diagnosed in presence of one of the following criteria: (a) hydronephrosis grade 1-3 in ultrasonography; (b) anteroposterior diameter of renal pelvis ≥10 mm; and (c) caliectasis with invisibility of distal ureter in the DTPA renal scan.

Sterile urine samples were taken by suprapubic method from the study subjects. Urine specimens were kept at -70°C under standard condition. Urinary level of TGF-β_1 was measured by quantitative sandwich ELISA method (Emax Immunoassay System, #G7590, Promega Corporation, Madison, USA). Urine creatinine was also measured for glomerular filtration rate (GFR) calculation by the Jeffe's modified technique using Synchorn C × 7 System (Beckman Instrument, Inc, USA). GFR was calculated then for every subject in order to assess the renal function by the following formula: GFR (ml/min/1.73 m^2) = k × height (cm)/serum creatinine (mg/dl). Defined values for k were as follows: for low birth weight or premature children, 0.33; for term infants, 0.45; for children and young girls, 0.55; and for young boys, 0.7.

Statistical analysis

The statistical analyses of the data were conducted using PASW (version 18.0, Chicago, IL, USA). Continuous variables were reported as means ± standard deviation and nominal variables were described as number/percentage. For intergroup comparisons, Chi-square test and Student *t*-test were used for comparing group means. Pearson correlation analysis was used to test the correlation of the variables where appropriate. A P value < 0.05 was considered significant.

RESULTS

In this study, 25 (male = 16; mean age = 7.4 ± 4.5 years) children with confirmed unilateral UPJO were compared with 25 (mean age = 6.8 ± 5.6 years) healthy peers matched for age and sex. GFR was significantly lower in the UPJO group (P = 0.01). General characteristics of the study population are summarized in Table 1.

Mean urinary level of TGF-β_1 was significantly higher in the UPJO children as compared with the healthy group (P = 0.001). On the other hand, mean level of urine TGF-β_1 increased with the increase in the grade of hydronephrosis (P = 0.0001). Comparison of the urinary level of TGF-$\beta_1$with the anteroposterior diameter of the ureteropelvic junction revealed than

Table 1: General characteristics of the study population

Characteristic	UPJO (n=25)	Control (n=25)	P value
Age	7.4±4.5	6.8±5.6	0.3
Male gender	16 (80)	16 (80)	-
GFR	112.4±10.1	123.29±4.4	0.01
Urine TGF-β1	87.1±12.6	30.5±14.5	0.001

GFR: Glomerular filtration rate, TGF: Transforming growth factor-beta 1, UPJO: Ureteropelvic junction obstruction

TGF-β_1 in patients with a diameter of 10-15 mm was 84.3 ± 10.3 and in patients with a diameter >15 mm was 92.8 ± 15.3; however, this difference was not statistically significant (P = 0.09).

DISCUSSION

This study aimed to identify the relationship of the severity of UPJO with the urinary level of TGF-β_1 in children who presented to our clinic as compared with healthy peers. UPJO is mostly diagnosed with invasive methods; however, a considerable number of patients remain undiagnosed until they present with profound renal dysfunction. Therefore, the need for a noninvasive and simultaneously sensitive diagnostic method is strongly felt in the clinical setting. Thus, urinary biomarkers seem to have the capability to become a suitable diagnostic measure for obstructive disorders of urinary tract.

Recent studies have shown that urinary biomarkers, such as TGF-β_1, rise due to renal injury and, therefore, can be a noninvasive and reliable handy tool for in-time confirmation of the diagnosis of UPJO.

Hydronephrosis and urinary tract obstruction can progress toward correction or deterioration and thereafter renal dysfunction. Superior urinary tract responds to obstruction by initiating a cascade of molecular and histological changes which lead to the activation of rennin-angiotensin-aldosterone system and elevation of TGF-β_1. TGF-β_1 is a cytokine normally produced in the urinary tract of healthy individuals and rises in pathological cases, particularly VUR and hydronephrosis.[2]

A very pioneer study observed that production of TGF-β_1 in urine was constantly and positively correlated with chronic renal dysfunction. Therefore, the elevation of this cytokine can be interpreted as the activity of the clinical situation or its chronic status and vice versa. One study reported the increase of the urinary level of TGF-β_1 in patients with UPJO. It also showed that the elevated levels of TGF-β_1 decrease subsequent to surgical operation and treatment of the obstruction.[13]

Based on our study, mean urinary levels of TGF-β_1 in children with UPJO were significantly higher than that of the normal controls matched for age and sex. Our findings were in line with previous similar studies.[2,14,15] Also, we observed that the level of TGF-β_1 in urine increases with the increase in the severity of hydronephrosis. This finding is justified by the hypothesis that the inflammation of the renal tissue augments by the increase in the intensity of hydronephrosis.

Our results showed a decrease in the GFR of the UPJO patients which explains that prolonged obstruction and thereby increased inflammation and molecular disturbances can result to tissue damage. Despite the tissue injury and even GFR reduction, there was no statistically significant correlation between the diameter of the ureteropelvic junction and the level of urinary TGF-β_1. Nonetheless, the observed positive trend may imply this fact that a larger study population would maybe help to clarify this correlation.

CONCLUSION

In brief, our findings suggest that measurement of urinary TGF-β_1 can be a good diagnostic tool for UPJO in children. Further studies are required to fully elucidate the cutpoint for diagnosis confirmation and exact relationship of the TGF-β_1 level with the degree of obstruction.

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