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ORIGINAL ARTICLE

Diagnostic significance of urinary transforming growth factor–β1 in the management of children with moderate to high grade pelvic-ureteric junction obstruction

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Abstract

Objective: The aim of the present study is to evaluate the role of urinary transforming growth factor – β1 (uTGF-β1) in congenital unilateral pelvi-ureteric junction obstruction (PUJO) upto the point of developing conventional indications for surgery and after pyeloplasty with the aim to explore the development of targeted therapeutic strategies aimed at modulating its effects and attenuating renal fibrosis.

Methods: Sixty two children with unilateral pelvi-ureteric junction obstruction, consisting of 46 boys and 16 girls, with a mean age of 9.4 months forms the study group. Twenty three out of 62 (37.1%) developed indication for surgery after a mean follow-up of 24.2±3.7 months. The uTGF-β1 levels have been measured by ELISA at different points of intervals, i.e., before indications for surgery, at the development of indications for surgery and after surgical intervention and compared with children continued to follow-on without indications for surgery.

Results: In children, who were continued to be followed up without indications for surgery, 39 had a mean baseline uTGF-β1 levels of 698.4mg/pg/Cr. which increased to 753.1mg/pg/Cr. (p valuie <0.001) after a follow-up of 24.1 months). As the children developed indications for surgery and subsequently underwent surgical intervention (n = 23), the mean uTGF-β1 baseline levels of 760.4mg/pg/Cr. were increased to 844.4mg/pg.Cr. just before the point of surgical intervention.

Conclusion: Urinary TGF-β1, hold the promise as a potential tool in the diagnosis and follow-up of hydronephrosis. The current evidence suggests that raised uTGF-β1 levels can effectively identify hydronephrosis with early parenchymal injury.

Keywords: uTGF-β1, Pelvi-ureteric junction obstruction (PUJO), Transforming growth factor-β (TGF-β)

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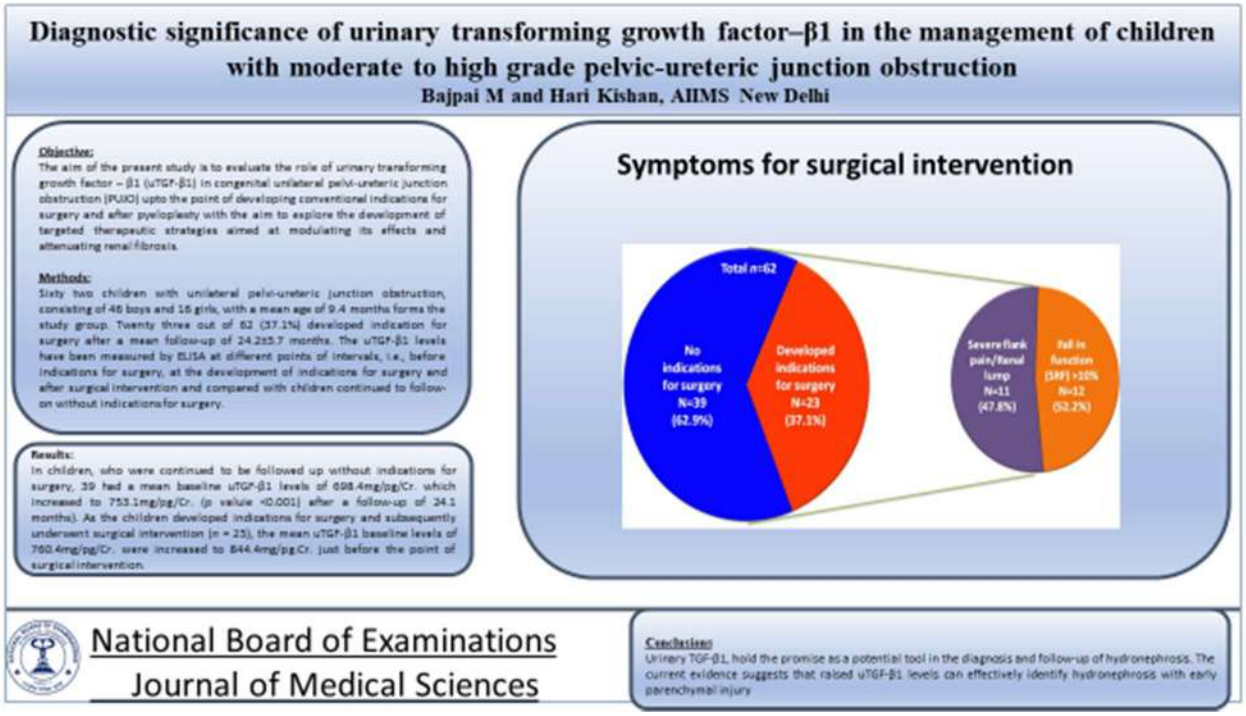
Graphical Abstract



Introduction

Transforming growth factor-β (TGF-β) has long been recognized as a key cytokine involved in the pathogenesis of renal inflammation and fibrosis [1]. The TGF-β superfamily encompasses a range of proteins, including TGF-βs, activins, inhibins, growth and differentiation factors (GDFs), bone morphogenetic proteins (BMPs), and glial-derived neurotrophic factors (GDNFs) Among the TGF-β isoforms found in mammals, there are three major forms: TGF-β1, TGF-β2, and TGF-β3 [2]. TGF-β1, in particular, has been extensively studied and is considered a profibrotic mediator in various kidney diseases [1]. Its role in promoting fibrosis is well established, as it can stimulate the production of extracellular matrix components, such as collagen, and inhibit the breakdown of existing extracellular matrix. This can lead to the accumulation of fibrotic tissue in the kidneys, impairing their normal function. The involvement of TGF-β1 in renal inflammation and fibrosis suggests that it may play a critical role in the progression of kidney diseases. Understanding the mechanisms by which TGF-β1 contributes to these processes can potentially lead to the development of targeted therapeutic strategies aimed at modulating its effects and attenuating renal fibrosis.

The challenges faced by urologists in managing fetal and postnatal hydronephrosis, particularly due to pelvi-ureteric junction obstruction (PUJO). It emphasizes the importance of accurate diagnostic tools to identify cases requiring surgical intervention and to assess renal function deterioration [3]. The current management criteria for PUJO rely on various diagnostic modalities, including serial ultrasonography, diuretic renogram, 99mTc dimercaptosuccinic acid (DMSA) scintigraphy, and excretory urography. The negative response to diuretic stimulation and renal function loss are indicators for surgical intervention i.e. pyeloplasty. The diuretic renogram, despite its invasiveness and use of ionizing radiation, is

commonly used for clinical evaluation of hydronephrosis. Moderate to severe grade hydronephrosis may lead to parenchymal function deterioration which will recovered or plateaued after pyeloplasty. Some patients experience continued renal function decline even after pyeloplasty. This unpredictable course of PUJO necessitates the availability of simple and accurate diagnostic tools to detect early renal function deterioration caused by obstruction before it becomes irreversible [4-6].

The pathophysiology of obstructive uropathy involves complex mechanisms that alter the expression of different growth factors. Growth factors play a role in renal wound healing processes. Urinary TGF-β1 has been associated with both normal and pathological conditions of the urinary tract, including vesicoureteral reflux and hydronephrosis. The aim of the present study is to evaluate the role of Urinary TGF-β1 in congenital PUJO before indications for surgery, at the development of indications for surgery and after pyeloplasty in operated group and to measure the levels of urinary TGF-β1 at the diagnosis and at the completion of study tenure in patients without indications for surgery. Additionally, we correlate this cytokine levels with other traditional markers such as DTPA, DMSA, glomerular filtration rate (GFR), grading of hydronephrosis as per society for foetus urology (SFU), serum creatinine (S.Cr.) and plasma renin activity (PRA) to get insights into the pathophysiology and management of PUJO.

Methodology

This prospective case-control study conducted at Department of Paediatric Surgery, All India Institute of Medical Sciences, New Delhi on patients registered in Wednesday Paediatric Urology Clinic from January 2015 to December 2019.

A total of 93 antenatal diagnosed hydronephrosis patients were initially assessed for inclusion in the study. However, 31 patients were excluded in which 14 cases were bilateral hydronephrosis, 10 had secondary vesico-ureteric reflux, 4 had multicystic kidney disease, 2 had horshoe kidney and one had poly cystic kidney disease. Therefore, the final sample population included 62 patients, consisting of 46 boys and 16 girls, with a mean age of 9.4 months (SD±5.0 months; range: 1 month to 18 months). These patients were matched with 10 controls. (Table 1). The study enrolled patients with unilateral PUJO only. The diagnosis of PUJO has been made on the basis of prenatal and postnatal ultrasonography findings, with the patients exhibiting normal renal function and receiving antibiotic prophylaxis. Twenty three out of 62 (37.1%) developed indication for surgery after a mean follow-up of 24.2±3.7 months (range 18 to 32 months). In 23 children developed indication for surgery 12 had a fall in SRF by >10% and 11 had severe flank pain or abdominal lump. This information outlines the characteristics of the study population, the inclusion criteria, and the initial presentation of the patients with PUJO.

As per the treatment protocol various imaging investigations have been performed to assess the patients with suspected or diagnosed ureteropelvic junction obstruction (PUJO). The inclusion criteria for imaging required ultrasonography showing moderate to gross dilatation of renal pelvis and calyces. The severity of hydronephrosis has been classified into grades III to IV, following the SFU classification [7]. The Tc-99m-DTPA plasma clearance by SPSM (true GFR) has been calculated as per the Russel's method: In this equation, the values of A and B are calculated using the variable T, which represents the sampling time in minutes. The calculations for A and B are as follows:

$A = -0.278T + 119.1 + 2450/T$ $B = 2.886T - 1222.9 - 16820/T$

Table 1. Demographic characteristics of the recruited children

1.	Number of patients	*n*=62
2.	Age [Mean±SD (Range)]	32.1±3.7 (1–84 months)
3.	Follow-up [Mean±SD (Range)	46.0±5.4 (36–61 months)
4.	Gender Male (%) Female (%)	 46 (74.2%) 16 (25.8%)
5.	Side of obstruction Right (%) Left (%)	 33 (56.5%) 27 (46.5%)
6.	Grade of hydronephrosis Gr. III (%) Gr. IV (%)	 21 (33.9%) 41 (66.1%)

The values of D and P should be provided in counts per minute (cpm), and T should be the sampling time in minutes (180 min in this case).

Blood samples were taken to assess the PRA levels and serum creatinine (Cr) values. PRA was measured by radioimmunoassay using a commercially available kit. (Normal PRA range according to the age —1–12 months = 4–8 ng/ml/hour; 1–3 years = 1–9 ng/ml/hour; 3–6 years = 1–5 ng/ml/hour. Cr was assessed by the kinetic enzymatic method at 6 monthly interval. The concentration of urinary TGF-β1 was measured using a commercially available quantitative sandwich enzyme-linked immunoassay (ELISA) kit. Standard curves were created, and the values obtained were expressed as pg/mL.

Healthy controls – Children with no renal pathology at the time of the enrollment of the patients who consented for the enrollment were considered healthy controls. The absence of renal pathology was confirmed by laboratory tests (renal function) and a renal ultrasonography. Urine samples from controls were collected by spontaneous voiding after completing the imaging tests and analyzed following the same procedures as in the case of the obstructive hydronephrosis group.

Statistical analysis - Data were analyzed with Statistic software package SPSS version 26 qualitative variables were expressed as percentages and quantitative variables as mean ± standard deviation. To compare two quantitative variables with normal distribution of data, a compare means student t-test analysis has been used and for operated group where measures are more than two a repeated measure ANOVA has been applied. $P < 0.05$ (CI 95%) was considered statistically significant. The protocol was approved by the Institute Ethics Committee at All India Institute of Medical Sciences, New Delhi 110029.

Results

Twenty three patients underwent Anderson-Hynes dismembered pyeloplasty, which was performed by a single surgeon (MB).

Histological findings confirmed the presence of obstruction in the obstructed segment of the PUJO patients. The typical pattern of PUJO, characterized by muscle hypertrophy/hyperplasia, collagen deposition, subepithelial fibrosis, and mild inflammatory infiltrate, was observed in 16 patients. Seven patients had an uncertain PUJO pattern, which was characterized by vascular congestion, edema, and mild inflammatory infiltrate with lymphocytes being predominant.

In patients with non-operative management (n=39) a consistent rising trend has been observed in the PRA and uTGF-β1 (p.value <0.001). (Table 2) In the postoperative follow-up, a significant decrease in urinary TGF-β1 and PRA values was observed. The control group consisted of 20 children (14 boys and 6 girls) without renal pathology at the time of preoperative evaluation. The mean age ± SD of the control group was 22.0±9.2 months (12-36 months). The mean uTGF-β1 concentration in the children with PUJO, as measured in the baseline urine samples, were significantly higher compared to the control group. The PUJO children had a mean concentration of 721.4pg/mg/Cr.±144.2, while the control group had a mean concentration of 113.5pg/mg/Cr. ± 16.6 ($p < 0.0001$).

In children, who were continued to follow-up without indications for surgery, 39 had a mean baseline uTGF-β1 levels of 698.4±159.2 which increased to 753.1±170.9 (p.valuie <0.001) after a follow-up of 24.1±3.93 (range 18-36 months). On the other hand, in children who developed indications for surgery and subsequently underwent surgical intervention (*n*=23), the mean uTGF-β1 levels at baseline were 760.4±105.5 which increased to 844.4±142.5 just before surgical intervention. This trend indicates that the children who are candidates for surgery have higher levels of uTGF-β1 at presentation as compared to those needing a period of observation (Table 2). After surgery, the mean uTGF-β1 concentration in the postoperative samples fell down significantly, as compared to the mean preoperative concentration. The postoperative mean concentration was 427.4±88.1, while the preoperative mean concentration was 844.4±142.9 ($p < 0.0001$). The uTGF-β1 levels are significantly associated with raised PRA in, both, the non-operated as well as the operated groups. This correlation was also not found to be significant with SRF & GFR. levels in the conservatively follow-on patients but significantly correlated with SRF and GFR in those who later developed indications for surgery. The uTGF-β1 levels did not show a correlation with creatinine levels in both the groups (Table 3).

A cut-off point for uTGF-β1 was determined as 104.7 pg/mg Cr., which was derived from the third quartile of uTGF-β1 levels measured in healthy controls. Patients with a uTGF-β1 level above 104.7 pg/mg Cr. had a 4.25-fold relative risk (RR) (95% confidence interval, 1.08-10.01) of having functional loss compared to patients with levels below 104.7 pg/mg Cr.. We have found that there was a linear correlation between the percentage of relative renal function loss and uTGF-β1 levels in patients with who developed indications for surgery. On the other hand, the study evaluated whether there was a linear correlation between the consistent rise in PRA and uTGF-β1 levels. The results showed no significant relationship between the serum creatinine and uTGF-β1.

Table 2. Changes in different parameters of upper tract damage between patients developed indication for pyeloplasty and patients without indications for surgical intervention.

Parameters	Patients with no indication for surgical intervention (*n*=39)	Patients developed indication and underwent pyeloplasty (*n*=23)
SRF		
Initial	43.7±2.9	43.4±3.3
Final	42.4±3.5	35.2±5.4
Df. with 95% CI*	1.4 (0.4, 2.3)	8.2 (6.5, 9.3)
P.value	0.007	0.001
GFR		
Initial	97.7±16.4	88.3±13.0
Final	95.4±11.6	69.7±12.3
Df. with 95% CI*	2.3 (-2.0, 6.7)	18.6 (14.3, 22.1)
P.value	0.285	0.001
S. Cr.		
Initial	0.7±0.2	0.7±0.3
Final	0.7±0.3	0.9±0.3
Df. with 95% CI*	-0.06 (-0.2, 0.04)	-0.1 (-0.3, 0.02)
P.value	0.256	0.082
PRA		
Initial	7.1±2.5	13.0±6.6
Final	11.2±4.7	17.5±7.1
Df. with 95% CI*	-3.1 (-4.4, -1.8)	-4.5 (-6.3, -2.8)
P.value	0.001	0.001
uTGF-β1		
Initial	698.4±159.2	760.4±105.5
Final	753±170.9	844.4±142.5
Df. with 95% CI*	54.6 (-76.9, -32.9)	-84.0 (-124.8, -43.2)
P.value	0.001	0.001

*Difference with 95% Confidence Interval (Lower and Upper)

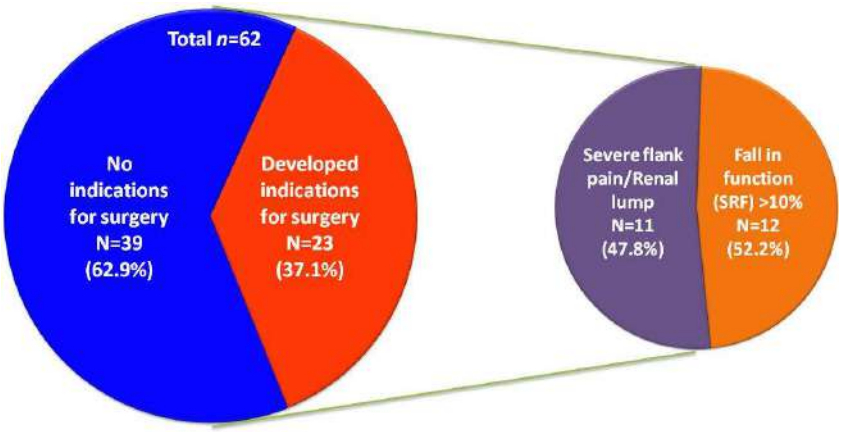


Figure 1. Symptoms for surgical intervention

Table 3. Impact of surgical intervention on renal function parameters including uTGF-β1 and PRA.

Mean±SD	**uTGF-β1**	**SRF**	**GFR**	**PRA**
A. Baseline	760.4±105.5	43.4±3.3	88.3±13.0	13.9±6.6
B. Pre-operative	844.4±142.5	35.2±5.4	69.7±12.3	17.5±7.1
C. Post operative	427.4±88.0	40.9±6.6	86.7±7.5	4.7±1.3
A–B Df*	-84.0 (124.8, -43.2)	8.2 (6.5, 9.3)	18.6 (14.3, 22.1)	-4.5 (-6.3, -2.8)
P.Value	**<0.001**	**<0.001**	**<0.001**	**<0.001**
B–C Df*	417.0 (355.5, 478.6)	-5.7 (-7.5, -3.9)	-17.4 (-23.3, -11.6)	12.8 (9.8, 15.9)
P.Value	**<0.001**	**<0.001**	**<0.001**	**<0.001**

* Df = Difference 95%CI (Lower, Upper)

Correlation between PRA and uTGF-β1

In our previous studies, specifically focused on PRA as an early prognostic marker of renal damage, we have reported that kidneys with higher levels of PRA have an increased probability to functional loss in children with hydronephrosis. The same applies for uTGF-β1 [9-11]. In another study, we have shown, that, patients followed nonoperatively had an increase in plasma renin activity (PRA), decrease in split renal function and glomerular filtration rate (GFR) as compared to controls. However, these changes were more significant in the group of patients who underwent pyeloplasty, during the pre-operative follow-up [12].

Specifically, in the operated group, mean PRA increased by 64.7% between the initial measurement (15.9 ng/ml) and the immediate preoperative measurement (26.2 ng/ml). Following surgery, PRA levels fell in all & returned to normal in the majority. On the other hand, in the nonoperatively followed patients, PRA continued to rise throughout the follow-up period. These findings suggest, that, raised PRA is reflective of obstructive stress in the tubulo-interstitial compartment which is present even in children followed non-operatively. In the present study, uTGF-β1 also reflected the same impact. However, all patients showed a significant decrease by 49.4% in uTGF-β1 (from 844.4 to 427.4 pg/mg Cr.) levels after surgical intervention but plateaued at higher levels with none reaching the normal range as compared to the controls (Figures 2 and 3).

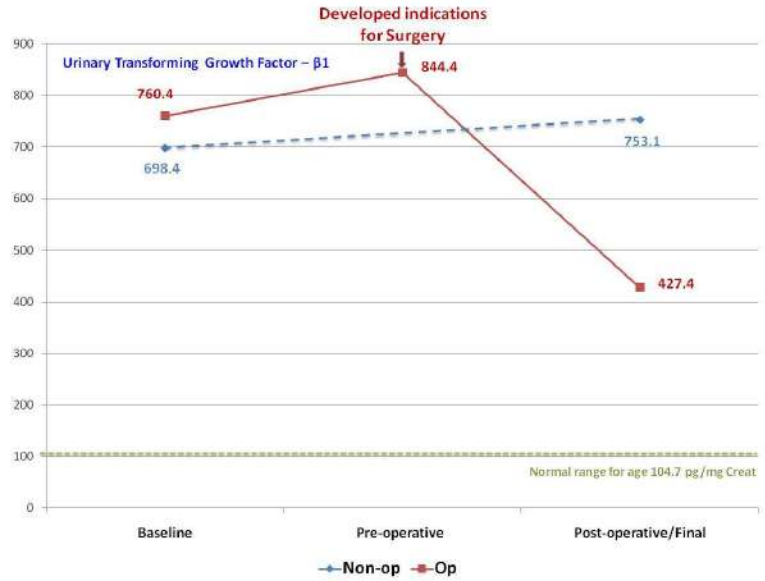


Figure 2. Outcome of uTGF-β1 in children with and without indications for surgery (baseline and final for non-operated group and baseline, pre-operative and post operative in children who underwent surgical intervention)

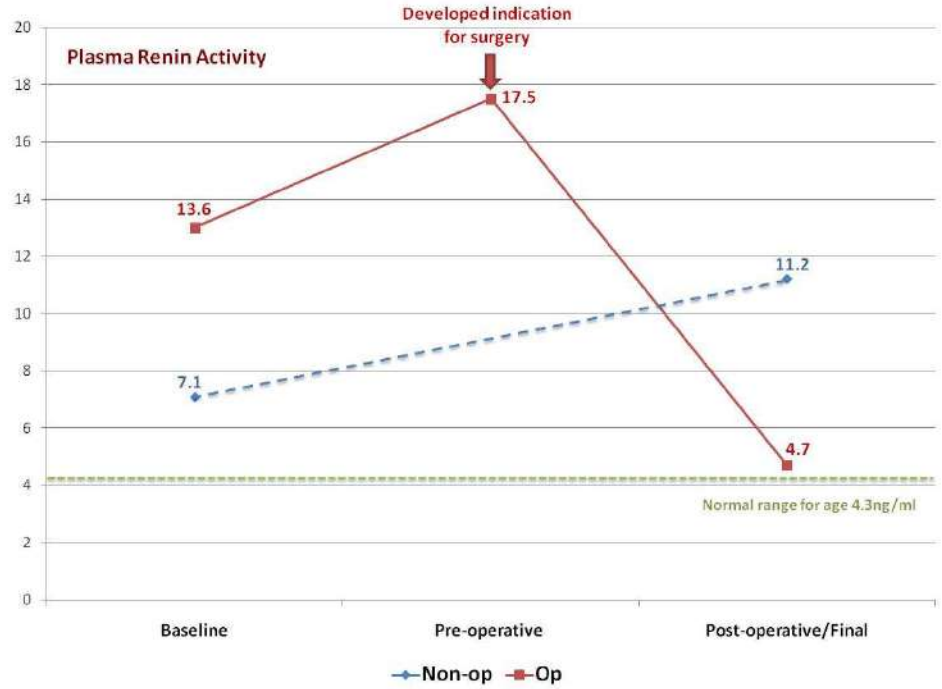


Figure 3. Outcome of PRA in children with and without indications for surgery (baseline and final for non-operated group and baseline, pre-operative and post operative in children who underwent surgical intervention)

Discussion

In cases of hydronephrosis, renal ultrasonography plays an important role in determining the characteristics of the condition, such as the appearance of the renal parenchyma, the diameter of the renal pelvis, and the status of the calyces. These factors help in determining the grade of hydronephrosis. However, it is important to note that the current markers of renal function detect obstruction significantly later in the natural history. There is no controversy, that, once obstruction is diagnosed surgery is the only treatment. However, search for the discriminatory factor which could distinguish between obstructed cases requiring surgery from those who would not has eluded the urologists for almost 4 decades. As a result, serial ultrasound studies are being performed over a period of time to assess any changes or progression of the condition [13]. Currently, diuretic renography is commonly used for the diagnosis of hydronephrosis, and it is preferred over excretory urography due to its lower radiation exposure and lack of nephrotoxicity. However, there are limitations to its diagnostic accuracy, particularly in cases of partial excretory response. Various factors, such as renal maturity, patient hydration, distensibility and volume of the collecting system, and the presence of a bladder catheter, can influence the results of the diuretic renogram [14].

Given the limitations and variability in the diagnostic tools for hydronephrosis [15], there is a need to detect renal injury at an early stage and have effective diagnostic and follow-up tools that are easy to use, reproducible, reliable, and minimally invasive, especially in pediatric populations. In recent years, there have been significant advances in understanding the pathophysiology of obstructive uropathy, particularly the role of pro-inflammatory components. These advances may contribute to the development of improved diagnostic and monitoring approaches for hydronephrosis [16]. Obstruction of the upper urinary tract triggers a series of molecular and histological events. One of the key pathways involved is the renin-angiotensin system, which becomes activated in response to the obstruction. This activation leads to the expression of profibrotic cytokines and transcription factors, including tumor necrosis factor-α (TNF-α), nuclear factor-κB (NF-κB), and transforming growth factor-β1 (TGF-β1) [17].

uTGF-β1, in particular, plays a significant role in the pathogenesis of renal fibrosis in cases of congenital hydronephrosis. Studies have shown that TGF-β1 protein and gene expression are predominantly localized in the proximal tubular cells of the kidney affected by hydronephrosis. It is believed that the process of epithelial-to-mesenchymal transition (EMT) is a major contributing factor to the development of renal fibrosis in congenital hydronephrosis. EMT refers to the transformation of epithelial cells into mesenchymal cells, which possess migratory and invasive properties. This transition is associated with the loss of cell-cell adhesion molecules and acquisition of mesenchymal markers. In the context of hydronephrosis, EMT contributes to renal fibrosis, leading to structural changes and functional impairment of the affected kidney [18]. TGF-β1 is a cytokine with a molecular weight of 25 kDa and is composed of two subunits connected by a disulfide bond. It is initially synthesized as an inactive prohormone. The active form of TGF-β1 binds to the type-II TGF-β receptor, leading to the activation and phosphorylation of the type-I TGF-β receptor. The activated type-I receptor, along with the TGF-β transcription-regulating complex, then translocates into the nucleus, where it exerts the effects of TGF-β1 [19].

The primary function of TGF-β1 is the regulation of extracellular matrix deposition and fibrinogenesis. It stimulates the proliferation of fibroblasts and induces the production of

collagen, proteoglycans, laminin, and fibronectin. TGF-β1 also inhibits collagenase, which is an enzyme that breaks down collagen. Furthermore, TGF-β1 inhibits fibrinolysis by promoting the production of plasminogen and its conversion to plasmin. It decreases the activity of metalloproteinases, which are enzymes involved in matrix degradation, and stimulates the production of protein receptors that attract macrophages. These activities of TGF-β1 contribute to fibrosis and the loss of renal function. In various urological and non-urological conditions, including vesicoureteral reflux and hydronephrosis, TGF-β1 can be excreted in the urine [20]. In another study, the concentration of TGF-β1 in bladder urine of patients with obstructive hydronephrosis was nearly three times higher than that in controls without renal pathology. Additionally, TGF-β1 levels in renal pelvic urine were found to be higher than in bladder urine [21].

These findings are consistent with previous studies conducted by Palmer et al. [22], Furness et al., [21] and El-Sherbiny et al. [23].

In terms of the correlation between preoperative radiographic studies and urinary TGF-β1, a correlation has been found between the percentage of relative renal function loss on DMSA scintigraphy and the level of intraoperative TGF-β1 [24]. However, no such correlation was found when comparing TGF-β1 with preoperative bladder urine, likely due to the dilution of TGF-β1 by urine from the contralateral kidney [25].

No difference has been found in urinary TGF-β1 levels, postoperatively, between patients with or without renal scars [26].

The study by Taha et *al*. demonstrated a significant increase in TGF-β1 values at one month post pyeloplasty, followed by a gradual decrease to significantly low levels one year postoperatively. The authors observed a significant decrease in bladder urinary TGF-β1 levels at three and five months after surgery, approaching values similar to those of controls without renal pathology. Additionally, there was a simultaneous decrease of almost 60% in hydronephrosis compared to preoperative values. These findings suggest that urinary TGF-β1 is not only useful for the diagnosis of upper urinary tract obstruction but could also serves as a reliable biomarker for monitoring the progression of the disease, comparable to traditional markers. It is believed, that, a longer follow-up would not yield different results in terms of TGF-β1 concentration, although further decreases in renal pelvic diameter may be expected over time [27].

Our study involved two groups of children: one group continued to be followed up without indications for surgery, and the other group developed indications and underwent surgical intervention. In the group of children who continued to be followed up without surgery (n=39), the mean baseline levels of uTGF-β1 (transforming growth factor beta-1) were 698.4±159.2. After a follow-up period of 24.1±3.93 months (ranging from 18 to 36 months), the uTGF-β1 levels increased to 753.1±170.9 (p.value < 0.001). This suggests that in the absence of surgical intervention, there was an increase in uTGF-β1 levels over time. On the other hand, in the group of children who developed indications for surgery (n=23), (Fig. 1) the mean baseline uTGF-β1 levels at presentation were higher at 760.4±105.5. Immediately prior to surgery, the uTGF-β1 levels further increased to 844.4±142.5. Following surgical intervention, the postoperative mean uTGF-β1 concentration was significantly lower than the mean preoperative concentration. The postoperative concentration was 427.4±88.1, while the preoperative concentration was 844.4±142.9 (p < 0.0001). These observations imply, that, raised levels of uTGF-β1 above normal are indicative of obstructive stress which could be relieved only with pyeloplasty.

The study also found that uTGF-β1 levels were significantly associated with the protein-to-creatinine ratio (PRA) in both the non-operated and operated groups. However, uTGF-β1 levels did not show a significant correlation with serum creatinine (Cr) levels in either group. In the conservatively followed group, uTGF-β1 levels did not significantly correlate with the levels of serum creatinine (Cr), split renal function of the obstructed side and glomerular filtration rate (GFR). However, in the group that developed indications for surgery, uTGF-β1 levels significantly correlated with SRF and GFR, indicating a relationship between uTGF-β1 and renal function. Our study has also established a correlation between baseline to preoperative and preoperative to postoperative levels of plasma renin activity protein-to-creatinine ratio (PRA) and renal histopathological changes in unilateral pelviureteric junction obstruction (PUJO). This finding suggests that PRA levels can serve as an early indicator of renal injury in this condition. In our previous studies we have specifically highlighted the role of PRA as an early prognostic marker of renal injury. In our earlier studies, we have reported that kidneys with hydronephrosis & normal function on isotope renography but elevated PRA levels, if not operated early, are associated with risk of functional loss. These observations further underscore the predictive value of elevated PRA in the early identification of unilateral PUJO requiring surgery [8-10].

In the present study, uTGF-β1 (transforming growth factor beta-1) has been observed to play a similar role. The elevated levels of uTGF-β1 are indicative of renal injury and serve as a predictive factor in the early identification of cases needing surgery. No significant correlation was found between the chronological age of the patients and the levels of uTGF-β1 or the percentage of renal function loss. Our findings suggest that uTGF-β1 can be a valuable tool for diagnosing obstructive hydronephrosis.

Conclusion

Urinary TGF-β1, hold the promise as potential tools for the diagnosis and follow-up of hydronephrosis. The current evidence suggests that uTGF-β1 can effectively identify early parenchymal injury & serve as a maker of obstruction in in PUJO-type hydronephrosis. In the present study, it was also observed that plasma renin activity (PRA) progressively increased from the time of presentation to the time of surgery in children with ureteropelvic junction obstruction. Being an early player in the cascade of events following renin angiotensin system activation, PRA serves as an early marker of obstructive stress in the tubule-interstitial compartment. It is noteworthy that the levels of uTGF-β1 and PRA are altered prior to the changes in parameters of actual renal injury, such as split renal function and glomerular filtration rate (GFR). Thus, PRA can serve as an early indicator of renal dysfunction in the context of ureteropelvic junction obstruction. Following the surgical intervention (pyeloplasty), uTGF-β1 and PRA levels were reduced in all children. These findings highlight the early diagnostic, clinical utility of monitoring uTGF-β1 and PRA levels in antenatally diagnosed & postnatally confirmed, PUJO-Type hydronephrosis. By detecting changes in these markers early on, pediatric surgeons can intervene to prevent further renal injury and optimize patient outcomes.

Ethics declarations

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Conflict of interest: The authors declare that they have no competing interests.

References

1. Sureshbabu A, Muhsin SA, Choi ME. TGF-β signaling in the kidney: profibrotic and protective effects. Am J Physiol Renal Physiol. 2016 Apr 1;310(7):F596-F606.
2. Zhang YE, Newfeld SJ. Meeting report - TGF-β superfamily: signaling in development and disease. J Cell Sci. 2013 Nov 1;126(Pt 21):4809-13.
3. Csaicsich D, Greenbaum LA, Aufricht C: Upper urinary tract: when is obstruction obstruction? Curr Opin Urol. 2004; 14: 213-7.
4. Sager C, Lopez JC, Duran V, Burek C, Perazzo E. Transforming growth factor-beta1 in congenital ureteropelvic junction obstruction: diagnosis and follow-up. Int Braz J Urol. 2009 May-Jun;35(3):315-23; discussion 323-5. doi: 10.1590/s1677-55382009000300008. PMID: 19538767.
5. Salem YH, Majd M, Rushton HG, Belman AB: Outcome analysis of pediatric pyeloplasty as a function of patient age, presentation and differential renal function. J Urol. 1995; 154: 1889-93.
6. Kass EJ, Majd M, Belman AB: Comparison of the diuretic renogram and the pressure perfusion study in children. J Urol. 1985; 134: 92-6.
7. Fernbach SK, Maizels M, Conway JJ. Ultrasound grading of hydronephrosis: introduction to the system used by the Society for Fetal Urology. *Pediatr Radiol*. 1993;23:478–480.
8. Bajpai M, Kumar A, Tripathi M, Bal CS. Dorsal lumbotomy incision in paediatric pyeloplasty. ANZ J Surg. 2004 Jun;74(6):491-4.
9. Singh A, Bajpai M. Plasma rennin activity: Early indicator of renal injury in bilateral pelviureteric junction obstruction in children. Urol Ann. 2014 Oct;6(4):295-7.
10. Bajpai M, Singh A. Plasma renin activity: An early marker of progressive renal disease in posterior urethral valves. J Indian Assoc Pediatr Surg. 2013 Oct;18(4):143-6.
11. Bajpai M, Pal K, Bal CS, Gupta AK, Pandey RM. Role of plasma renin activity in the management of primary vesicoureteric reflux: a preliminary report. Kidney Int. 2003 Nov;64(5):1643-7.
12. Minu Bajpai, C.S. Bal, M. Tripathi, M. Kalaivani and Arun K. Gupta. Prenatally Diagnosed Unilateral Hydronephrosis: Prognostic Significance of Plasma Renin Activity. J Urol. 2007; 178(6): 2580-84.
13. Tomas Lence, Gina M. Lockwood, Douglas W. Storm, Caitlin E. Ward, Christopher S. Cooper. The utility of renal sonographic measurements in differentiating children with high grade congenital hydronephrosis. J Pediatr Urol. 2021; 17(5): 660.e1-660.e9,
14. Taylor AT. Radionuclides in nephrourology, Part 2: pitfalls and diagnostic applications. J Nucl Med. 2014 May;55(5):786-98.
15. Esmaeili M, Esmaeili M, Ghane F, Alamdaran A. Comparison Between Diuretic Urography (IVP) and Diuretic Renography for Diagnosis of Ureteropelvic Junction Obstruction in Children. Iran J Pediatr. 2016 Feb;26(1):e4293.
16. Rishor-Olney CR, Hinson MR. Obstructive Uropathy. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558921.

17. Klahr S. Urinary tract obstruction. Semin Nephrol. 2001 Mar;21(2):133-45.
18. Higgins CE, Tang J, Higgins SP, Gifford CC, Mian BM, Jones DM, Zhang W, Costello A, Conti DJ, Samarakoon R, Higgins PJ. The Genomic Response to TGF-β1 Dictates Failed Repair and Progression of Fibrotic Disease in the Obstructed Kidney. Front Cell Dev Biol. 2021 Jul 2;9:678524.
19. Poniatowski ŁA, Wojdasiewicz P, Gasik R, Szukiewicz D. Transforming growth factor Beta family: insight into the role of growth factors in regulation of fracture healing biology and potential clinical applications. Mediators Inflamm. 2015;2015:137823.
20. Makieieva NI, Morozova OO, Iarova KK, Pryima YS, Golovachova VO, Vygivska LA. URINARY EXCRETION OF TGF-B1 AND VEGF IN CHILDREN WITH VESICOURETERAL REFLUX. Wiad Lek. 2020;73(11):2411-2415.
21. Furness PD 3rd, Maizels M, Han SW, Cohn RA, Cheng EY. Elevated bladder urine concentration of transforming growth factor-beta1 correlates with upper urinary tract obstruction in children. J Urol. 1999 Sep;162(3 Pt 2):1033-6.
22. Palmer LS, Maizels M, Kaplan WE, Firlit CF, Cheng EY. Urine levels of transforming growth factor-1 in children with ureteropelvic junction obstruction. *Urology.* 1997;**50**(5):769–773.
23. El-Sherbiny MT, Mousa OM, Shokeir AA, Ghoneim MA. Role of urinary transforming growth factor-β1 concentration in the diagnosis of upper urinary tract obstruction in children. Journal of Urology. 2002;**168**(4):1798–1800.
24. Çelik T, Yalçin H, Günay EC, Özen A, Özer C. Comparison of the Relative Renal Function Calculated with 99mTc-Diethylenetriaminepentaacetic Acid and 99mTc-Dimercaptosuccinic Acid in Children. World J Nucl Med. 2014 Sep;13(3):149-53.
25. Cristian SagerJuan C. LopezVictor DuranCarol BurekErnesto Perazzo. Transforming growth factor-β1 in congenital ureteropelvic junction obstruction: diagnosis and follow-up. Int. Braz J Urol. 2009; 35(3): 315-25.
26. Aboutaleb H, Abouelgreed TA, El-Hagrasi H, Bakry Eldib D, Abdelaal MA, El Gohary MA. Correlation of Renal Scarring to Urinary Tract Infections and Vesicoureteral Reflux in Children. Adv Urol. 2022.
27. Taha MA, Shokeir AA, Osman HG, Abd el-Aziz Ael-A, Farahat SE. Diagnosis of ureteropelvic junction obstruction in children: role of endothelin-1 in voided urine. Urology. 2007 Mar;69(3):560-4