Journal of Pediatric Urology (2011) 7, 105—112

Journal of Pediatric urology

FETAL UROLOGY

Urinary biomarkers in prenatally diagnosed unilateral hydronephrosis

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Received 4 October 2010; accepted 2 December 2010
Available online 8 January 2011

KEYWORDS
Congenital hydronephrosis;
Ureteropelvic junction obstruction;
Biomarker;
Transforming growth factor beta 1;
N-Acetyl-beta-d-glucosaminidase;
Alkaline phosphatase;
Gamma-glutamyl transferase;
Monocyte chemotactic peptide-1;
Epidermal growth factor;
Endothelin-1

Abstract The introduction of prenatal ultrasonography as a screening method entails an increasing number of infants diagnosed with prenatal hydronephrosis. Ureteropelvic junction obstruction accounts for 35% of prenatal hydronephrotic cases. Urinary tract obstruction that occurs during early kidney development affects renal morphogenesis, maturation and growth, and in the most severe cases this will ultimately cause renal insufficiency. A major challenge in the clinical management of these patients is to preserve renal function by selection of the 15%—20% who require early surgical intervention, leaving those for whom watchful waiting may be appropriate because of spontaneous resolution/stabilization without significant loss of renal function. Today, this requires medical surveillance, including repetitive invasive diuretic renograms relying on arbitrary threshold values, and therefore there is a need for non-arbitrary, non-invasive urinary biomarkers that may be used as predictors for renal structural changes and/or decreasing renal function, and thereby provide the surgeon with more clear indications for surgical intervention. In this review, we summarize the currently well-known facts about urinary biomarkers in ureteropelvic junction obstruction concerning renal function, and we also suggest potential novel urinary biomarkers.

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1477-5131/$36
doi:10.1016/j.jpurol.2010.12.004

Introduction

Congenital urological anomalies are easily identified by prenatal ultrasonography [1,2], and the number of infants diagnosed with urological anomalies has increased after the introduction of prenatal ultrasonography as a screening method [3]. Hydronephrosis is the most common genitourinary tract anomaly detected in prenatal studies, and its prevalence depends on the criteria used for significant dilatation. A Danish review from 2006 showed that the prevalence of prenatal urological anomalies is 1%—2% with prenatal hydronephrosis being the most common anomaly (amounting to 0.5% in newborns). Ureteropelvic junction obstruction (UPJO) accounts for 35% of prenatal hydronephrotic cases [4]. Urinary tract obstruction that occurs during early kidney development affects renal morphogenesis, maturation and growth [5], and in the most severe cases this will ultimately entail progressive renal tubular atrophy and interstitial fibrosis with loss of nephrons [6]. In bilateral cases, in turn, this will cause renal insufficiency and will require dialysis treatment and eventually kidney transplantation.

Therefore, obstructive nephropathy is a notable cause of renal failure in infants and children. A major challenge in the clinical management of patients is to select the 15%—20% of children who require early surgical intervention in order to preserve renal function, from those for whom watchful waiting may be appropriate because of a high frequency of spontaneous resolution/stabilization without significant loss of renal function.

Today, the most commonly used indicators for operative treatment are: 1) declining function of the hydronephrotic kidney by more than 5%, and to less than 40% of the total renal function estimated by radionuclide examinations, 2) ipsilateral flank pain, 3) frequent pyelonephritis, 4) massive hydronephrosis, and 5) social indications (e.g. the patient does not attend the regular medicals) [4]. The concern is that there may be a tendency toward performing redundant operations, or observing for too long so that the low kidney function, especially in older age groups, causes health problems [7]. The effects of UPJO on kidney structure have been described in unipapillary kidney models such as guinea pigs and rats [8—11] and in the human-like polypapillary pig kidney with hydronephrosis induced before nephrogenesis has been completed [12]. Anni Eskild-Jensen et al. have shown that obstruction is associated with impaired nephrogenesis causing a significant reduction in the number of nephrons formed. Although the decreased obstructed kidney function later normalizes, they suggest that the structural changes may in later years affect renal function and reduce the functional capacity of the kidney [12].

Accordingly, there is a need to find more exact predictors of renal structural changes and/or short-term and long-term development of decreasing renal function. Non-invasive urinary biomarkers may generate early measures of renal injury and functional impairment [13], and thus the use of such predictive biomarkers may provide us with clearer indications for surgical intervention. In this review, we summarize the currently well-known facts about urinary biomarkers in significant UPJO concerning kidney functional development, and we also review potential novel urinary biomarkers.

Cellular response of the developing kidney to urinary tract obstruction

Addressing the need for new and safe non-invasive biomarkers requires a basic understanding of the pathophysiology of congenital obstructive nephropathy [14].

After acute unilateral obstruction of a ureter, a transient increase in blood flow to the kidney is followed by a prompt reduction in renal blood flow, mediated by increased renal vascular resistance of primarily the preglomerular arteriole. This is caused by a complex and so far not completely understood contribution from various vasoactive mediators including angiotensin [15], thromboxane A2 [16], and endothelin [17] among others. Subsequently, an interstitial inflammatory response is initially characterized by macrophage infiltration, tubular dilatation and renal tubular apoptosis, leading to tubular atrophy and interstitial fibrosis with loss of nephrons [8]. The process is mediated by the release of cytokines, chemokines and growth factors, which are signaling molecules (proteins or peptides) acting as intercellular mediators in the process of paracrine communication [9]. This is a complex system with interaction of a variety of both locally and systemically produced molecular products.

Potential new biomarkers are found among these molecules involved in macrophage recruitment and proliferation, and tubular death and survival [8]. Concentrations of a number of the molecules involved in these processes are measurable in the urine during a UPJO. To explore the potential pathophysiological impact of these compounds in congenital obstructive nephropathy, a large number of animal studies have been performed, giving promise for the identification of several molecules as potential urinary biomarkers, and some of these have also been tested in clinical studies (Table 1).

Transforming growth factor beta 1 (TGF-β1)

TGF-β1 is synthesized from renal tubular epithelial cells, macrophages and interstitial fibroblasts [18], and it is the main modulator of the healing process after tissue injury [19]. It is a profibrotic cytokine, which has been reported to play an important role in the changes seen in response to obstructive nephropathy [20—23]. Palmer et al. were the first to show that TGF-β1 is elevated in pelvic and bladder urine from children with unilateral obstructed kidneys [24]. TGF-β1 concentration is also increased in the renal tissue in children with UPJO [25,26]. Several later studies confirmed the three to four-fold increased concentration of urinary TGF-β in children with severe unilateral hydronephrosis compared to control subjects [19,27,28]. Furness et al. also showed that this bladder urinary marker correlates with upper urinary tract obstruction and is more than 90% sensitive [27]. They included 30 children (from 1 month to 17 years old, mean age 5 months) who underwent surgery for obstructive hydronephrosis. In all children, hydronephrosis was grade 3 or higher according to the Society for Fetal Urology classification [29]. Twenty-six of the children were diagnosed when the renography revealed a prolonged half-time and/or an obstructed washout curve pattern during the diuretic phase. Obstruction was also diagnosed