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Review Article

Can bladder fibrosis in congenital urinary tract obstruction be reversed?

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Summary
A variety of conditions exists in adults and children in which functional or anatomical urinary tract obstructions cause bladder fibrosis, which reduces the bladder's ability to store and empty urine. Current surgical procedures include removal of the obstructions to facilitate bladder emptying or prompt prenatal or postnatal spinal closure to prevent further neurogenic damage. Bladder fibrosis may occur, and it can get worse if a flow hindrance persists or deteriorates. Anti-fibrotic therapeutic strategies that target a variety of factors have been developed in animal models, but currently there are no anti-fibrotic therapies available for clinical use. This review examines the pathogenesis of bladder fibrosis that is caused by congenital obstructions of the lower urinary tract, and it focuses on the principal signalling factors and potential treatment modalities.

Introduction

Congenital urinary tract obstruction (CUTO) accounts for most of the chronic kidney disease that occurs during childhood [1], and the obstructions are categorised into upper and lower urinary tract obstructions according to the obstruction site. Congenital upper urinary tract obstruction causes hydronephrosis, which is accompanied by abnormalities in the smooth muscle tissue of the pelvis and ureter that include fibrotic changes. Lower urinary tract obstructions result from anatomical and functional changes [2]. Posterior urethral valves (PUVs) are congenital anatomical obstructions of the urethra that can affect the bladder and the kidney. Less common causes of CUTO include urethral atresia, prune belly syndrome (PBS), and anterior urethral valves. Functional bladder obstructions are usually neurogenic, and in the worst cases they are accompanied by detrusor-sphincter dyssynergia and a spastic bladder. Such urinary tract obstructions lead to high pressure in the bladder or the renal pelvis, and they have profound consequences that remodel bladder architecture and function [3]. The bladder wall hypertrophy and increased accumulation of extracellular matrix are the most notable consequences. Accumulating evidence shows that CUTOs induce permanent alterations, even after the obstructions have been mitigated [2]. As there are no effective therapies available to manage these fibrotic changes, there is a significant unmet medical need.

This review examines the pathogenesis of fibrosis in the lower urinary tract, and it focuses on the principal signalling factors involved in fibrosis and offers potential treatment modalities.

Literature search

We searched the literature using the PubMed, Web of Science, Scopus, and Embase databases. The search terms were: 'congenital', 'fibrosis', 'obstruction', 'bladder', 'prevention', and 'reverse'. The literature search was restricted to English-language articles, with no date restriction applied. Ninety-five articles were reviewed, and 43 representative articles were listed for references based on the relevance to the review and the requirement of the *Journal of Paediatric Urology*. Additional references can be retrieved from the author.

Clinical relevance of congenital lower urinary tract obstruction

Congenital lower urinary tract obstruction (CLUTO) causes life-long morbidity or substantial perinatal mortality. PUVs are the most common anatomical cause of CLUTO (Table 1), and they are present in about 0.1 per 1000 live male births [4]. During prenatal ultrasound

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Table 1 Clinical diseases associated with common congenital lower urinary tract obstructions [1,43].

	Disease	No./10,000 live births
Most common anatomical diseases	Post urethral valves	1.4–2.1 (male)
	Prune belly syndrome	0.08–0.3
	Urethral atresia	0.3
Most common neurogenic disease	Neural tube defects	2.9–3.5
Other less common diseases	Anterior urethral valves	NA
	Urethral duplication	NA
	Urinary fistula	NA

NA, not applicable.

screening, bilateral hydronephrosis and bladder dilatation with or without oligohydramnios may give rise to a suspicion of CLUTO with a valve aetiology. A common sonographic finding is the 'keyhole sign', which comprises bladder distension and urethral dilation proximal to the valves. However, the specificity of this sign is low with a considerable false positive rate [1]. Urethral atresia describes a complete infravesical obstruction caused by a membrane that obliterates the lumen at the distal-most aspect of the prostatic urethra. PBS is characterised by abdominal wall flaccidity, cryptorchidism, and urinary tract abnormalities that include prostatic hypoplasia, urethral atresia, or stenosis [1].

Neural tube defects cause abnormal development of the spinal canal and the internecine spinal cord, and they have a worldwide incidence of 0.3–4.5 per 1000 births [5]. Neurogenic bladder dysfunction caused by neural tube defects, for example, myelomeningocele, sacral anomalies, and tethered chord, results in detrusor-sphincter dysfunction, which affects the bladder's ability to store and empty urine. The functional status of the detrusor muscle and external sphincter whether spastic or flaccid can lead to different consequences. Most worrisome is detrusor-sphincter dyssynergia resulting from spastic detrusor and spastic sphincter leading to a functional obstruction. Both anatomical and functional obstructions induce infravesical flow hindrances that result in abnormally high bladder pressures. CLUTOs damage both the lower and upper urinary tracts.

Persistent high bladder pressure causes hypertrophy and hyperplasia of the smooth muscle and changes in its contractility. *In vitro* studies have shown that stretch to the bladder smooth muscle cells results in increased expression of various growth factors, including epidermal growth factor, nerve growth factor [3]. In addition, Metcalfe et al. found that progression of fibrosis is accompanied by increased levels of insulin-like growth factor 1 and connective tissue growth factor in rats subjected to partial obstruction [6]. Long-term obstructions also contribute to damage of the ureterovesical junction, which causes reflux and hydronephrosis. The failure to empty urine into the amniotic cavity results in oligohydramnios, which causes pulmonary hypoplasia and may lead to foetal death.

During the early obstruction period, the smooth muscle layer is maintained, unlike obstruction of the upper urinary tract, in which hydronephrosis, cortical cysts, and dilated medullary ducts are evident. Prolonged obstruction induces smooth muscle hypertrophy and collagen deposition, leading to decreased bladder compliance [7], and finally a fibrotic and an acontractile bladder [1]. Only limited information is available from human foetus studies; however, it is not known whether the changes are the same as those found in the adult population.

Findings from a study of bladders from foetuses with PUVs [8] showed that the obstructions caused marked increases in the thicknesses of the bladder walls and that the smooth muscle tissues and the connective tissue depositions were relatively normal. Such structural changes account for the bladder's dysfunction, which involves mixed urodynamic patterns that comprise myogenic failure with overflow incontinence, an overactive bladder, and a small poorly compliant bladder [9].

Various animal models have been studied; however, results from these require careful interpretation as a single animal model is less likely to reproduce the complex changes observed in humans. For example, female animals are used for bladder outlet obstruction (BOO) models, but BOO is more prevalent in men. Also, procedures around the bladder neck are highly likely to injure nerve innervation to the bladder.

In sheep foetuses at 60 days of gestation, complete urinary tract obstruction for 4 days caused an initial thinning of the bladder wall that was followed by marked thickening of the bladder wall accompanied by detrusor muscle hypertrophy and extracellular matrix (ECM) accumulation after obstruction for 14 days [10]. However, Farrugia et al. studied sheep foetuses and reported that short-term complete obstruction over 9 days initiated a rapid growth respond with maintained contractility. In contrast, extending to 30 days of obstruction produced more prominent ECM deposition and hypo-contractility [11]. In animal models, partial urinary tract obstruction causes hypoxia within the bladder wall, which is accompanied by angiogenesis [12]. During the compensated stage of bladder obstruction, the tissues replace the contractile apparatus with non-muscle isoforms, and synthesis and deposition of collagen increase [13]. End-stage bladder decompensation involves destabilisation of bladder function and a fibrotic bladder is formed that has no contractile function [14]. The transition from compensated to decompensated obstructive bladder disease could be attributed to specific changes in the balance between the cells and their ECM. Fibrosis formation in the bladder is also observed in elderly people, which may be associated with ischaemia or obstruction (i.e. benign prostate hyperplasia in males) [15].

Fibrosis in the bladder

Fibrosis is characterised by scarring caused by excessive production and deposition of ECM components. This process usually takes place over many months and years, and it can cause organ dysfunction.

Fibrosis is thought to develop when the normal wound-healing response fails to stop [16]. During wound healing, the mesenchymal fibroblasts become active and they migrate into the damaged tissue where they produce

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