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RESEARCH ARTICLE

MICRO ANATOMY OF PELVI URETERIC JUNCTION AND ITS CHANGES IN HYDRONEPHROSIS

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ABSTRACT

The concept of the pelvi ureteric junction has been there for more than a century and yet there is no clear anatomical definition of this junction. Pelvi ureteric junction (PUJ) obstruction is an impedance to the urine flow from the renal pelvis to the ureter. It occurs in 1:1000 to 2000 newborns and is the commonest cause of obstructive uropathy in children.1 The pathophysiology of pelvi ureteric junction obstruction in unknown. The knowledge of histologic changes and innervations at UPJ is necessary for proper understanding of patho physiology and its correlation with the functional outcome after pyeloplasty. This systematic review addresses the question of whether the human pelvi ureteric junction is a discrete anatomical entity and changes seen in PUJ obstruction.

Methods: A systematic literature review was undertaken to investigate the normal gross and microscopic anatomy of the pelvi ureteric junction and histopathological changes at pelvi ureteric junction in patients with PUJ obstruction using the electronic databases MEDLINE, PubMed, Cochrane Library and Google Scholar

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INTRODUCTION

During embryogenesis, the ureter arises from the ureteral bud and extends towards the area of parenchyma that will become the kidney. The PUJ forms during week 5. Induction of the metanephric blastema has been thought to be mediated by the ureteral bud through transcription factors such as Pax-2 and by growth factors such as c-ret, kdn-1, and wt1, as well as by TGF-β. By weeks 10-12 of gestation, the initial tubular lumen of the ureteric bud becomes canalized and urine can pass from glomerulus to urinary bladder (Stephen and Kingm, 1992). At physiologic rates of urine production, the calyces and renal pelvic musculature contracts at a frequency greater than that of the upper ureter. The pelvis gradually fills with concomitant rise in the intrapelvic pressure and this continues until the pelvic pressure exceeds upper ureteric pressure. The urine then flows into the upper ureter. It has been suggested that the ureteropelvic and ureterovesical portions of the ureter are the last to canalize; thus, failure of the process to complete would lead to partial canalization. Theory for the development of an obstructive process suggests premature arrest of ureteral wall musculature development leading to the persistence of an aperistaltic segment at the level of the PUJ, thus preventing normal propulsion of urine down the ureter. Intrinsic obstruction is noted as ureteral narrowing. In these cases, the ureter is solely involved and the lumen is, in general, narrowed but open.

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Early in development, the proximal ureter is folded on itself, and persistence of the infolding may contribute to the kinked appearance of the proximal ureter. The most attractive theory is that the obstruction is secondary to muscular discontinuity, which disrupts the coordinated motion of smooth-muscle cells and may result in impeded peristalsis propagation across the PUJ and interference with urine bolus formation in the proximal ureter. This absence or disorientation of smooth-muscle fibers at the PUJ is clearly evident on electron microscopy, with the findings of rearrangement and widely separated smooth-muscle cells, excessive collagen fibers, and increased elastin in the adventitia, combined with diminution of nerve terminals and nerves at the stenotic portion. Problems with this narrow but structurally patent lumen of the PUJ may not be evident under low workloads (ie, low urine volumes into low bladder pressures) but become apparent as a consequence of inability to adjust efficiently to increased workloads (high urine volumes or high bladder pressure).In all likelihood, intrinsic PUJ obstruction may be caused by a variety of factors, which may have both biochemical and mechanical etiologies. Another theory proposes that improper innervations with diminished synaptic vesicles may be a factor in the development of PUJ obstruction .The role of some of the transcription and growth factors in the etiology of PUJ obstruction remains to be elucidated. The exact nature of the abnormality is controversial.

Normal Histology: Anatomy and histology of the ureter is not constant along its length. The ureter is characterized by three

histological layers, namely an external adventitia, a smooth muscle layer and an inner mucosal layer (Cormack, 1986).

The Adventitia

It forms the outermost layer of the ureteric wall and consists of loose fibroelastic connective tissues which merges with the surrounding retroperitoneal areolar tissue. It consists of elongated fibrocytes, collagen, elastic fibrils with blood vessels, nerves and lymphatics.

Muscle Coat

The muscle is located between adventitia and submucosa. Throughout the length, the muscle coat of the ureter is fairly uniform in thickness and measures 750-800 microns in width. Intervening connective tissue are minimal. Morphologically distinct longitudinal and circular layers cannot be distinguished (Cormack, 1986).

The Mucosa

The ureter is lined by an urothelium, on the external aspect of which is a layer of subepithelial fibroelastic connective tissue, the lamina propria. Histological study of normal ureter by various workers revealed a wide variety of conflicting observations on the arrangement of ureteric smooth muscle. Two separate coats of muscle consisting of longitudinal layer surrounded by a thinner circular layer have frequently been described (Gosling, 1970; Notley, 1971). A division of upper part of the ureteric muscle into thin longitudinal layers on inner and outer aspect of middle circular coat has also been recorded (Notley, 1971). In contrast Sappey, Droff, Woodburne asserted that muscle fibres were grouped into bundles which crisscrossed in all directions and communicated with one another and a reciprocal exchange of fibres leading to difficulty in distinguishing separate layers of circular and longitudinal fibres (Gosling, 1970). Schneider and Caraudo proposed that muscle bundles formed interlacing series of spirals and specifically mentioned their inability to distinguish histologically the junctional region between the renal pelvis and ureter (Gosling, 1970). The transition from the pelvis into the ureter is associated with a slight increase in thickness of the muscle coat and the transitional epithelium is thrown into longitudinal folds which project into the lumen (Gosling, 1970). Most authors have failed to detect an anatomical pelvi ureteric junction although Satani, Youseff reported thick circular muscle in the region (Gosling, 1970). Hana *et al.,* 1976 noted that ureteropelvic junction is histologically ill defined and the upper abdominal ureter had a relatively thin muscle wall. Muscle bundles of different orientation lay side by side and the ureteral muscle consisted of braided bundles of muscles fibers arranged in interlacing spirals (Hana *et al.,* 1976). Kench *et al*. noted smooth muscle bundles of the renal pelvis and upper ureter to run a spiral course with individual bundles contributing at different level, to both of the inner and outer muscle coats (Kench, 1982). Starr *et al.,* 1992 found muscle fibres whose predominant orientation was circular in uretero pelvic junction with a few inner and outer longitudinal fibres (Starr *et al.,* 1992). Notley *et al.,* 1971 had shown that ureter had an extensive ramification of unmyelinated nerve fibers throughout all the layers of the ureter, barring the epithelium but no ganglion cells were seen. Hana *et al.* 1976 had shown that each nerve bundle was composed of unmyelinatted vesiculated (adrenergic) and empty (cholinergic) axons that were invaginated into Schwann cells. Neurohistochemical investigation by Elbadwi, Shenck and Schulman *et al*. however indicated the presence of ganglia in the pelvic ureter (Schulman, 1972). The unmyelinated nerve fibres depart from the plexus and eventually contact or approach the surfaces of smooth muscle cells as varicosities as noted by Angevine, 1986; Kobyashi, 1987. Nerves having immunoreactivity to various neuropeptides have been demonstrated in the innervation of ureter by tyrosine hydroxylase, vasoactive nerves. Different layers of ureter may be indepedently controlled by different population of nerves (Edyvane *et al.,* 1995).

Histopathological changes in pelvi ureteric junction obstruction

Current research shows that histological changes in congenital hydronephrosis can be found in PUJ mucosa and muscularis. The exact nature of histopathological abnormality is controversial in PUJ obstruction. Examination of the defective segment in congenital hydronephrosis has been reported as stenosed or the muscle as inappropriately oriented (Hinman, 1970). Foote *et al.,* 1970 found agenesis or reduction in muscles in UPJ with congenital hydronephrosis. However hypertrophy is considered to be the standard reaction of smooth muscle to increase work load in UPJ obstruction. Cusen noted a fourfold increase in the area of the smooth muscles as compared to control values in the specimens of UPJ obstruction (Cassen and Tymms, 1972). In experimental studies of ureteral obstruction, muscle hypertrophy was noted after 3 days of obstruction whereas hyperplasia took 7 days to develop (Gee and Kiviat, 1975). Both light and electron microscopy have demonstrated excessive collagen as a cause for the indistensibility of the UPJ in obstruction (Hana *et al.,* 1976; Allen. 1970). Kaneto *et al.* 1991 has studied the growth related changes in UPJ and found that there is a change from the circular pattern of muscular arrangement in neonates to oblique arrangements in children which were ambiguous or lacking in UPJ obstruction. He also demonstrated segmental muscular hypoplasia, disarrangements of bundles or lack of longitudinal muscle fibres and concluded that the presence of a fibrotic segment at the UPJ can block the downward transmission of peristalsis. In the pelvis of hydronephrotic kidney an increase in lamina muscularis, presence of collagen fibres between muscle fascicles, variable amount of elastin in adventitia and lamina muscularis. At the pelvi ureteric junction the abnormalities were, increase in the number of inner longitudinal muscle bundles, increased collagen between muscle bundles. The percentage area density of smooth muscle in the obstructed versus normal was increased (Starr *et al.,* 1992). Pinter *et al.,* 1997 demonstrated atrophy of the smooth muscle in the obstructing UPJ and its replacement with collagen. There was associated muscular hypertrophy proximal to the obstructing UPJ. They provided a histopathologial classification of the resected uretero pelvic segment.

Group 1 PUJ (almost) normal

Group 2 Lumen of the PUJ moderately compressed. Circular and longitudinal muscles fibres in the junction easily recognizable. Only a moderate accumulation of collagen. Mild muscular hypertrophy proximal to PUJ.

Group 3 Lumen of PUJ narrowed and compressed. Circular and longitudinal muscles discernible. Accumulation of collagen in the submucosa and definitive muscular

hypertrophy in the wall of the renal pelvis, proximal to the PUJ.

Group 4 Lumen narrowed with extreme thickening of the wall of the PUJ. Marked smooth muscle atrophy with pronounced collagen accumulation. Easily recoginable smooth muscle hypertrophy in the wall of the pelvis adjacent to PUJ.

Group 5 PUJ with practically no lumen and with an extremely thickened wall. Excessive collagen infiltrates the wall of PUJ, only compressed smooth muscle remnants visible. The wall of the pelvis proximal to the junction is thickened with advanced smooth muscle hypertrophy.

Masahi *et al.,* 1997 studied the PUJ complex in cases of obstruction and found that muscle fascicles were spares and thin, intercellular spaces were six to seven times wider than control. Collagen fibrillar sheath of smooth muscle cells and the interstitial collagenous component were dense. They concluded that in intrinsic PUJ obstruction, the interestitial collagen fibres formed more compact and rigid structures, without normal wavy bundle formation, thus restricting mobility and resiliency of the PUJ. Due to thick collagen fibrillar sheath, the variability and contractility of smooth muscle cells were arrested (Masahi *et al.,* 1997). In pathologically impaired tissue nerve fibers can be found in the adventitia and submucosa, but these are lacking in the muscle layer. By contrast, the normal tissue reveals plentiful nerve of fibers in the submucosa, adventitia, and a lesser amount – in the muscle layer. Interstitial cells of cajal (ICC)s have been contemplated generally, concentrating on the potential part of these cells in pathogenesis of intrinsic hydronephrosis. It is found that human PUJ contains Cajal cells indistinguishable to those found in the gastrointestinal tract. These are shaft molded cells with restricted cytoplasm, substantial core and two cytoplasmic processes (Wojciech Apoznanski *et al.,* 2013). Confinement of ICCs is for the most part limited to the muscle layer, and particularly, to the whole shape of the roundabout circular muscle layer. The patients with pelvi ureteric junction obstruction show not very many if any of ICCs, in spite of the fact that reports distributed on this matter are exceptionally dubious (Metzger *et al.,* 2004). As per Apoznanski *et al.,* a number of ICCs was not statistically different analyzing graded age groups of pediatric PUJ, though, Koleda *et al*. examine demonstrated that various Cajal cells in hydronephrotic patients is higher than that of normal subjects. Furthermore, these creators discovered abatement in Cajal cells alongside maturing, though, the expansion is clarified by an underlying compensatory component that stops by time

Conclusion

In most individuals there is a gradual transition between the renal pelvis and ureter with no external features indicating the presence of a discrete pelvi ureteric 'junction'. Internally, however, luminal mucosal folds are prominent in this region. There is no consensus on the arrangement of muscle fibers at the pelvi ureteric junction. Depiction of histopathology of congenital hydronephrosis accessible in the literature is quite clear. The commitment of the urothelium changes to the pathogenesis of pelvi ureteric junction stays indistinct. The most common structural changes revealed are include atrophy and dysfunction of myocytes, increased accumulation of extracellular matrix accompanied by interstitial collagen deposition, and diminution of innervations. Each of these changes can significantly affect pelvi ureteric junction function.

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