Cases - Ehlers-Danlos syndromes: Review on the urologic implications

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INTRODUCTION

KEY MESSAGES

- Ehlers-Danlos syndromes (EDS) are a group of inherited connective tissue disorders associated with significant morbidity and mortality.
- Patients with EDS are often reported to have urologic issues, despite this there is limited literature addressing the relationship between EDS and urologic conditions, as well as specific considerations for management.
- Urologists should adopt a multidisciplinary approach to management for patients with EDS, as well as personalized followup.
- Further research is needed to better understand the urologic implications of EDS and to inform best practices in management.

Ehlers-Danlos syndromes (EDS) are a group of heterogeneous inherited connective tissue disorders that are associated with significant morbidity and mortality.[1] The prevalence of EDS is reported between 1 in 5000 and 1 in 100,000 depending on the subtype, with the most common subtype of EDS being the hypermobile variant (type III).[2] Clinical features of EDS include hypermobility of joints, skin hyperextensibility, as well as connective tissue fragility, especially in ligaments, blood vessels, and hollow organs.[1] EDS are multi-system disorders and complications of EDS can include joint dislocations, chronic pain, fatigue, and, more critically, arterial and organ rupture.[3] Given the prevalence of connective tissue in the urinary tract and the presence of abnormal collagen in the pelvis with EDS there are reported associations with urinary pathology specifically urinary incontinence, pelvic organ prolapse, pelvic pain syndrome, bladder diverticulum, vesicoureteral reflux, and recurrent urinary tract infections (Figure 1).[4-13] There is a lack of clarity on the clinical significance and prevalence of these urologic conditions in patients with EDS. This narrative review discusses two EDS patient cases and reviews the literature on the relationship between EDS and urologic conditions.

CASE REPORTS

Case 1

A 24-year-old male with EDS presented with urinary retention. On initial assessment he described progressive symptoms, including urinary frequency every 30 minutes, nocturia every two hours, urgency, a sensation of incomplete emptying, and frequent feelings of bladder fullness. He denied recurrent urinary tract infections (UTIs), dysuria, or hematuria. He had previously tried oxybutynin, tamsulosin, and tolterodine, but without symptom relief. At the time of consultation, he was taking mirabegron 25 mg and solifenacin 10 mg. He had also tried pelvic floor physiotherapy, which was not helpful.

The patient had not undergone formal imaging to assess urinary retention, as he was homebound due to his severe comorbidities, and no further workup, including cystoscopy or urodynamics, had been performed. Following the initial consultation, home care nursing was arranged to measure his post-void residuals using an in-and-out catheter. He reported performing clean intermittent catheterization (CIC) a few times per week, with residual volumes ranging from 400 to 500 mL. With CIC, his lower urinary tract symptoms resolved completely, and he had no issues with UTIs. He is currently doing well, and is satisfied with his management, performing CIC several times per week with mirabegron 25 mg (he stopped solifenacin 10 mg).

Case 2

A 23-year-old woman with EDS presented with lower urinary tract symptoms. She reported a chronic history of infrequent voiding, urinating only every two to three days due to minimal bladder sensation. Prior to the initial consultation, she was found to have elevated post-void residuals in the 700 mL range. Due to limited mobility and significant pain, she was unable to perform clean intermittent catheterization (CIC), and a suprapubic catheter was inserted to manage her retention. At the time of consultation, she also reported hesitancy, straining, dysuria and pelvic pain.

Cystoscopy revealed no anatomical abnormalities or obstruction. Urodynamics demonstrated an obstructive voiding pattern, intermittent detrusor overactivity, and normal bladder compliance. She voided 187 mL at a maximum flow rate of 5.3 mL/s, with an elevated detrusor pressure of 51 cm H2O. During follow-up, various management options were discussed, including sacral neuromodulation, or urinary diversion. Ultimately, the patient decided to continue with the suprapubic catheter, which is changed regularly. She continues to experience recurrent UTIs, which are managed with antibiotics.

Urinary incontinence

Urinary incontinence (UI) as defined by the International Continence Society is the involuntary loss of urine.[13] There are five subtypes of urinary incontinence including stress, urge, mixed, functional and overflow incontinence. UI is a bothersome condition with the prevalence of UI in the general population ranging between 25-45%, stress urinary incontinence (SUI) between 4-35% and urgency urinary incontinence (UUI) between 11%-16%.[14-16] The prevalence of UI is

higher in documented to be higher in women and increases with advancing age. [16] The prevalence of UI in patients with EDS is reported to be higher with several studies estimating between 50-69%.[8,17,18] Furthermore, the prevalence of SUI and UUI have also been reported to be significantly higher in patients with EDS as compared to patients without, with the prevalence of SUI ranging from 40-76% and UUI between 40-70%.[5,6] Overflow incontinence is common in EDS patients, a result of the ability of their bladder to stretch up to 3L with normal function, whereas in the general population bladder distention up to 2L can lead to urinary retention.[8] This highlights the importance of identifying and treating urinary incontinence in patients with EDS, given the significant impact of urinary incontinence on quality of life and the sequalae of chronic urinary retention on recurrent urinary tract infections, urolithiasis, and renal function. With respect to overactive bladder, it is suspected that patients with EDS are more likely to have an overactive bladder because of dysautonomia or nervous system dysfunction. However, there is limited available literature. Overall, there is a paucity of research on the pathophysiology of urinary incontinence types other than overflow incontinence in patients with EDS, and data on the age of onset of UI in this population remains limited. Interestingly, animal studies have shown that changes in bladder wall collagen can increase bladder sensitivity in rat models.[19] Further, limited literature exists on specific considerations in the management of urinary incontinence in this population. It is likely however that this population would benefit from pelvic floor physiotherapy in the treatment of incontinence as they have pelvic floor laxity. There is no data in the literature for considerations of minimally invasive therapies (e.g. onabotulinumtoxinA injections and neuromodulation).

Pelvic organ prolapse

Pelvic organ prolapse (POP) is the descent or herniation of pelvic structures into the hymenal ring secondary to ligament or muscular weakness. The prevalence of POP is approximately 40% in the general population and 13-75% in patients with EDS.[20-22] Women with EDS are thought to be more likely to develop POP because of their pelvic floor laxity. Several studies have shown that patients with EDS and POP were diagnosed earlier, were more symptomatic and had a poorer quality of life compared to patients without EDS.[8,23-25] Additionally, one study by Davidson et al. found that patients with EDS and other hereditary disorders of connective tissue (HDCM) who underwent surgery for POP (e.g. anterior repair, posterior repair, sacrocolpopexy, mid-urethral sling, etc.) were more likely to have postoperative complications (e.g. urinary retention >1 week, hematoma, ileus, fever, and wound complications) and have an increased rate of hospital readmission related to the index surgery (46% and 10% of patients respectively). However, the authors did not find a difference between patients with and without EDS concerning the recurrence of POP postoperatively.[26] Patients with EDS will often have other comorbidities which may present challenges for surgical planning and management.

Pelvic pain syndrome
Chronic pain is one of the most frequent symptoms found in patients with EDS, with close to 90% of patients reporting pain.[27]

Pain gynecological in nature
Patients with EDS have also reported vulvodynia, vestibulodynia, dyspareunia, and generalized pelvic pain. A retrospective cohort study that investigated gynecologic symptoms in 386 women with hypermobility type EDS found a high prevalence of dyspareunia (43%) compared to patients without EDS (3-18% in the general population).[28-29]

Bladder diverticulum
Bladder diverticulum is defined as the herniation of the bladder mucosa through the muscularis propria of the bladder wall.[30] The overall prevalence of bladder diverticular in the general population is approximately 10%.[31] Bladder diverticula is either congenital or acquired, with acquired diverticula being most common among older men.[32] Many bladder diverticula are asymptomatic and discovered incidentally during investigations for other conditions.[32] Most of the literature on bladder diverticula and EDS are published case reports. In these case reports patients had other symptoms and/or urological clinical conditions including UI and vesicoureteral reflux.[33-35] Interestingly, there is a report of one patient who was initially diagnosed with EDS who became pregnant and had a bladder diverticulum that became symptomatic as it was complicated by urinary retention and urinary tract infection as the pregnancy progressed.[35]

Vesicoureteral reflux
Vesicoureteral reflux (VUR) is defined as the non-physiological retrograde flow of urine from the urinary bladder to the upper urinary tract (e.g. ureters and kidney).[36] In one cohort study of 313 children it was observed that the prevalence of joint hypermobility was higher in children with VUR as compared to the general population.[37] Additionally, a case-control study that included 50 children found that those with a history of VUR were significantly more likely to have EDS than the control group (24% vs 6.7% respectively).[38] The authors hypothesize that the abnormal composition of the connective tissue in the urinary tract system may contribute to the severity of the (pre-existing) VUR phenotype in these patients.[38] Further, Tokhmafshan and colleagues examined 50 children with VUR and discovered a significantly higher prevalence of joint hypermobility among these patients, with 57.7% of girls and 66.7% of boys affected, compared to only 1-25% in the general population with VUR.[39]

Recurrent urinary tract infections
Recurrent urinary tract infections (rUTIs) are defined as two documented UTIs within six months or three in one year according to the American Urological Association (AUA).[40] The etiology behind rUTIs in patients with EDS is thought to be multifactorial with the prevalence of rUTIs reported to be higher in patients with EDS at 24% compared to the general population (6-

10.5%).[40-41] There is one case report which reported a child with EDS and recurrent urinary tract infections.[42]

The role of the urologist

Patients with Ehlers-Danlos Syndrome (EDS) frequently present with early-onset or severe urologic conditions, including pelvic organ prolapse, urinary incontinence, recurrent urinary tract infections, and bladder pain. Urologists should consider EDS in younger patients with unexplained or refractory pelvic floor symptoms, particularly those with a history of tissue fragility or joint hypermobility. A brief screen for hypermobility and connective tissue features can help identify patients who may benefit from referral to rheumatology if not already diagnosed. Coordination with primary care is essential to support ongoing monitoring, reduce unnecessary antibiotic use for functional symptoms, and ensure comprehensive multidisciplinary management. Surgical planning should consider the increased risk of perioperative complications. Optimal care often requires collaboration with pelvic floor physical therapists and pain specialists. Further research is needed to clarify the prevalence of EDS in high-risk urologic populations and to develop evidence-based guidelines for management.

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FIGURES AND TABLES

Figure 1.