The endocrinology of the urinary bladder

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Abstract

The urinary bladder primarily functions as a reservoir for urine. Apparently, it serves only a mechanical and passive role in the urinary tract, but closer scrutiny reveals that it has several meaningful endocrine interactions. This vital organ has an intricate plexus of neurons that release neurohormones concerned with the functioning of the bladder. Endocrine disorders, most notably diabetes, can cause a broad spectrum of bladder dysfunction. The current review explores the bladder as a source of neurotransmitters, a target for organ damage due to uncontrolled endocrinopathy, a beneficiary of hormonal therapy, and a tool to improve endocrine health.

Keywords: Urinary bladder, diabetes, lower urinary tract symptoms, overactive bladder, urinary obstruction.

DOI: 10.47391/JPMA.23-100

Introduction

The urinary bladder is usually thought to have a mechanical role, with its primary function limited to receiving, storing, and releasing urine. This notion is untrue. The bladder contains an intricate network of neurons that express a wide array of neuropeptides and neurotransmitters[1] Although the autocrine role of these neurotransmitters and hormones is well-proven, their systemic effects might be a subject worth pondering. The bladder and its neuromuscular network are susceptible to various systemic insults, including maladaptation from endocrine derangements. On the other hand, hormonal modulation is a recognized approach to improving bladder dysfunction. In this review, we discuss the important endocrine connections of the urinary bladder.

Neurotransmitters and neuropeptides in the bladder

The urinary bladder contains a rich plexus of neuro-ganglionic structure that regulates the act of voiding. Acetylcholine released from the parasympathetic postganglionic axons in the pelvic nerve induces bladder contraction to facilitate micturition. Noradrenaline from sympathetic postganglionic neurons relaxes bladder muscles and contracts urethral muscles to inhibit micturition. Parasympathetic postganglionic nerves also release adenosine triphosphate, which excites bladder muscle, and nitric oxide (NO), which relaxes the urethral muscle.[2] The ganglia in the bladder show immunoreactivity to vasoactive intestinal peptide, NO synthase, neuropeptide Y, galanin, and occasionally to tyrosine hydroxylase.[1] Though the bladder does not secrete any hormones systematically, rare cases of the tumoral proliferation of chromaffin tissue of the sympathetic nerves in the urinary bladder wall have been described. These pheochromocytomas of the bladder can secrete catecholamines causing episodic hypertension, palpitation, and micturition syncope.[3]

Diabetes and bladder dysfunction

Bladder dysfunction can be an accompaniment of several endocrine disorders, including diabetes. A combination of factors interacts in diabetes to cause a varied spectrum of bladder abnormalities. Detrusor muscle defects, autonomic neuropathy, and urothelial dysfunction can lead to functional and structural changes, resulting in diabetic cystopathy. The cystopathy is attributed to small muscle fiber damage independent of atherosclerosis.[4] The classic symptoms of diabetic cystopathy are decreased bladder sensation, increased bladder capacity, and impaired bladder emptying with resultant increased post-void residual volume.[5] Recurrent urinary infection is another common complication of diabetes.

Bladder dysfunction associated with other endocrinopathies

Graves' disease is associated with interstitial cystitis and manifests as bladder pain syndrome.[6] Uncontrolled hypogonadism is often associated with lower urinary tract symptoms (LUTs). Rare endocrine diseases such as Wolfram Syndrome, characterized by diabetes mellitus, optic atrophy, diabetes insipidus, and sensory-neural hearing, can have bladder dysfunction in the form of neurogenic bladder with urodynamic abnormalities.[7] Many disorders of sexual development have associated developmental defects of the bladder. The common

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Table-1: Common endocrine disorder induced bladder dysfunction.

Endocrine condition	Bladder dysfunction
Diabetes mellitus	**Diabetic cystopathy** (classical description)/ Underactive bladder: Decreased bladder sensation, increased bladder capacity, impaired bladder emptying, increased post-void residual volume, urinary retention. **Overactive bladder:** Urgency, with or without incontinence, usually with urinary frequency and nocturia. **Voiding dysfunction:** Bladder outlet obstruction or urinary incontinence **Recurrent cystitis**
Hypothyroidism	Decreased voiding frequency, urinary retention
Hyperthyroidism	Urinary frequency, storage symptoms including urgency, urge incontinence, nocturia, and enuresis (either primary or secondary), voiding symptoms such as incomplete emptying and straining
Menopause	Urgency, frequency, recurrent lower urinary tract infection, dysuria, urinary incontinence
Obesity	Urolithiasis, lower urinary tract symptoms, female stress incontinence.

endocrinopathy-induced bladder disorders is summarized in Table 1.

Sex hormones and bladder function

Hormonal changes exert a significant impact on bladder structure and function. In females, estrogen strengthens the urinary tract and provides defense against bacterial infections. It regulates lower urinary tract motility as well.[8] Similarly, testosterone improves detrusor activity in men. Nocturia is prevalent among elderly men with benign hypertrophy of prostate and LUTs. Recent studies have demonstrated that low testosterone plays an essential role in the development of overactive bladder in elderly men.[9]

Bladder as a target for endocrine treatment

Menopause and female hypogonadism increase the risk of genitourinary problems with the potential to impact the quality of life. Estrogen replacement therapy helps manage symptoms of urinary frequency, urgency, and incontinence in postmenopausal women. Vaginal estrogen benefits the symptoms of an overactive bladder. Vaginal dehydroepiandrosterone (DHEA), systemic estrogen therapy, and ospemifene are also helpful.[10] The benefits of vaginal estrogen for stress urinary incontinence are inconclusive. Vaginal estrogen and DHEA are also shown to protect against recurrent urinary tract infections.[11]

Similarly, hypogonadal men who present with LUTs improve with testosterone supplementation. Testosterone increases bladder capacity and compliance and decreases detrusor pressure at maximal flow in men with late-onset hypogonadism.[12] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been suggested as a potential treatment for myogenic underactive bladder. This is based on the rationale that heart failure and "bladder failure" pathophysiology is similar in many ways.[13] Finally, desmopressin, a synthetic analogue of vasopressin, is an accepted treatment for nocturnal enuresis.[14]

Iatrogenic bladder dysfunction from endocrine drugs

In the last few years, SGLT2i has emerged as a ground-breaking therapy for diabetes, heart failure, and nephropathy because of its beneficial effect on cardiovascular and renal outcomes. Their primary mechanism of action is glycosuria, which also increases the susceptibility to genitourinary infection. LUTS, including urinary frequency, urgency, nocturia, and rarely incontinence, can occur with SGLT2i.[15] Pioglitazone was reported to increase the risk of bladder cancer, though a definite link has not been established.[16] Type 2 diabetes by itself increases the risk of several types of cancer, with some series reporting a 40% increased risk of bladder cancer compared to controls.[17] Metformin might reduce the incidence of bladder cancer and improve its prognosis.[18] A recent experimental study has shown that metformin exerts antitumour effect by inhibiting bladder cancer cell migration and growth and promoting apoptosis.[19]

Lower urinary tract symptoms as marker of endocrine health

Polyurea is one of the classic osmotic symptoms that occur with hyperglycaemia. In resource-limited settings, where regular screening facility is not available, polyurea is one of the most common identifying symptom of diabetes. It is also a marker for worsened glycaemic control if one is not on SGLT2i. Genitourinary symptoms frequently occur during and after menopause, and appropriate treatment can positively impact several health parameters. Polyurea and nocturia are also indicators of diabetes insipidus, which have recently been renamed as arginine vasopressin deficiency (AVP-D) (for central etiologies) and arginine vasopressin resistance (AVP-R) (for nephrogenic etiologies).[20] While manifestations of AVP-D can offer insights into pituitary health, AVP-R often provides valuable clues on systemic diseases and adverse drug effects.

Summary

The urinary bladder is much more than passive recipient and storage organ of urine. This review explores the broad spectrum of interconnections between the bladder and endocrinopathies. Bladder, while controlling the urine outflow function, gets affected in various endocrine states and is responsive to hormonal treatments. Diabetes, hypogonadism and thyroid can impair functioning of the bladder. Sex hormone replacement for hypogonadism in men and for perimenopausal symptoms in women can alleviate bladder symptoms. Antidiabetic agents can exert beneficial as well as detrimental effect on the bladder. A closer understanding of the endocrinology of bladder will optimize clinical outcomes.

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