



# Recent Perspectives for Clinical Problems of Lower Urinary Tract Dysfunction (LUTD) in Diabetes Mellitus (DM)

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## Abstract

Patients with diabetes mellitus (DM) tend to show high prevalence of lower urinary tract dysfunction (LUTD), including diabetic bladder dysfunction (DBD), diabetic cystopathy and overactive bladder (OAB). LUTD is observed in 43-87% of T1DM, and 25% of T2DM. Compared to non-DM, DM has 7.5 times more OAB. When OAB is found during urination and bladder contractility is found during urination, such complexed situation is called detrusor hyperactivity with impaired contractility (DHIC). Some treatments were observed such as pharmacotherapy and Botulinum toxin type A (BoNT-A) injection therapy. Recent research developments include low-intensity extracorporeal shockwave therapy (Li-ESWT) and electroacupuncture (EA).

**Keywords:** Lower urinary tract dysfunction (LUTD); Diabetic bladder dysfunction (DBD); Overactive bladder (OAB); Detrusor hyperactivity with impaired contractility (DHIC); Diabetes mellitus (DM)

## Commentary Article

Diabetes mellitus (DM) has been more prevalent across the world. DM has various complications of macroangiopathy and microangiopathy [1]. Among them, clinical problems on lower urinary tract have been observed. In recent years, overactive bladder (OAB) has been attracting attention. Compared to non-DM, DM has 7.5 times more OAB. Furthermore, the symptom is severe, and urinary urgency, pollakiuria, nocturia, and urge incontinence are observed in combination, which greatly affects QOL. Bladder outlet obstruction and detrusor muscle hypoactivity are also problems when urinating. Both of the above, are rather common in the actual practice. When OAB is found during urination and bladder contractility is found during urination, such complexed situation is called detrusor hyperactivity with impaired contractility (DHIC) [2]. It is often observed in DM patients, and the risk of urinary tract infection is also high with easier severe status.

Bladder dysfunction is observed in approximately 43-87% of T1DM, and 25% of T2DM. About 75-100% of diabetic patients with peripheral neuropathy had shown the presence of diabetic

cystopathy [3]. Bladder function has to be evaluated in diabetic patients associated with incontinence, pyelonephritis, recurrent urinary tract infections. Typical symptoms of lower urinary tract include frequent urination, nocturia, urgency and weak urinary stream. [3].

The major complications of diabetes are associated with microangiopathy, classically known as neuropathy, retinopathy, and nephropathy. Autonomic neuropathy may be systemic and cause cardiovascular, gastrointestinal and genitourinary dysfunction. Regarding the mechanism of urinary bladder control, several investigations have been found concerning humoral, neural and local factors. They include various symptoms of lower urinary tract dysfunction (LUTD), which is mainly related with diabetic neuropathy and from complex diabetic impaired function [4]. Some recent topics and fundamental information concerning LUTD would be described in the following.

LUTDs caused by diabetes are referred to as diabetic bladder dysfunction (DBD) or diabetic cystopathy. The DBD phenotype sometimes changes in the clinical progress. In early stage, it shows an increase in bladder volume and contractility. As it progresses, the symptoms will show diminished urinary urgency,

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increased residual urine volume, and flaccid bladder. According to recent reports on the combination of LUTD and urodynamic testing, there are some specific findings such as detrusor muscle overactivity, detrusor sphincter dysfunction and loss of micturition reflex.

Diabetic patients are characterized by poor bladder compliance and exit obstruction. For diabetic male, 57% showed LUTS and bladder outlet obstruction, which seemed to be twice incidence compared with non-DM male. Urinary incontinence is predominant in diabetic female, with urinary incontinence in 43% of 50-64 years and 51% of 65-80 years [5]. The risk is doubled compared to non-DM women. The risk is doubled compared to non-DM women. As A1c value increases for every 1%, incontinence increases by 13% and stress urinary incontinence increases by 34% for the period of 6.5-8.0% [2].

DM and OAB have been common health threats [6]. They show increased prevalence with advancing age. Bladder dysfunction with DM was analyzed for retinopathy and nephropathy [7]. Among them, diabetic patients with retinopathy showed significantly higher prevalence of DHIC. The diagnosis of DBD includes medical history, physical examination, and urodynamic testing, but it is clinically useful to apply a questionnaire. For the predictor of DBD diagnosis, diabetic history would be >9 years and HbA1c is >7.9% in male diabetics, and >8 years and >7% in female diabetics, respectively [8].

The goals of treatment for DBD are glycemic control, relaxation of LUTS, and maintenance of renal function. Recently, sodium-glucose co-transporter 2 inhibitor (SGLT2-i) have been widespread. Although the blood glucose level decreases, it should be noted that SGLT2-i shows a high diuretic effect associated with polyuria, nocturia, and urinary tract infection [9]. OABs with resistant to pharmacotherapy are eligible for surgical treatment. Botulinum toxin type A (BoNT-A) injection therapy is relatively easy to administer among invasive treatments. It is effective for improving OAB symptoms with or without DM and for eliminating detrusor hyperactivity in urodynamic testing. However, it should be noted that diabetic patients often have an increase in residual urine volume and malaise after treatment, and that the effective period is rather short for DHIC symptoms [2].

DM has been independent risk for OAB. DM-associated OAB has multifactorial and time-dependent elements from pathophysiological point of view. DBD is often associated with diabetic micro- and macro-angiopathy, such as diabetic neuropathy and atherosclerosis [2]. Both of persistent systemic and bladder urothelial inflammation may bring the onset of OAB. The relationship between OAB and atherosclerosis was studied for 147 females [10]. The numbers of patients and control numbers were 74 vs 71, in which HbA1c showed 6.00% vs 5.39%, respectively. All atherosclerosis indicators showed significant association with OAB and that there was a significant

relationship between OAB and decreased bladder neck perfusion. Thus, OAB microvascular disease may be involved in systemic atherosclerosis.

It is not clarified whether atherosclerotic risks other than DM may influence cytopathy (small fiber neuropathy of bladder) or not [11]. The associations of biomarkers in diabetic cystopathy were analyzed for 44 patients as to BMI, BP, glucose variability, nerve conduction, urodynamics and ultrasound Doppler echography. Consequently, urodynamic diabetic cystopathy did not correlate with these factors, suggesting that bladder small fiber neuropathy may act independently from various risks [11].

Recent research developments on diabetic bladder dysfunction (DBD) and/or diabetic cystopathy have been found in experimental trials using rat model. Diabetes rat is produced by the administration of streptozotocin [12]. According to previous reports, low-intensity extracorporeal shockwave therapy (Li-ESWT) on the bladder was developed and investigated. As a result, Li-ESWT brought the reduction of the expression of IL1b, Chrm2, and to a lesser extent Trpv1 for the control levels. This suggested the possibility of treatment modality for DBD [12]. Consequently, these basic reports will contribute clinical practice for diabetic patients with DBD. For chronic pelvic pain syndrome and erectile dysfunction, Li-ESWT has shown the safe efficacy for the therapy of various urological disorders [13].

The electroacupuncture (EA) has been reported to show efficacy for relieving DBD. However, little is known concerning the mechanism. Then, the effect of EA for DBD was investigated using streptozotocin-high-fat diet- (STZ-HFD-) induced diabetic rats [14]. Consequently, EA could reduce the hypertrophy of the bladder to decrease DBD. The mechanism includes i) reversing the impairment of bladder detrusor smooth muscle cells (SMCs) and mucosa layer, and ii) involving in the regulation of phospho-myosin light chain (p-MLC) and phospho-myosin light chain kinase (p-MLCK). In order to study the mechanism of DBD, KK-Ay mice were used to identify the expression of related genes [15]. As a result, KK-Ay mice can become a proper model to clarify DBD pathophysiology, where decompensated state may be from alternations of expression levels in Myosin Va, SLC17A9, P2X1, M3 and M2 [15].

## Conflict of Interest

The authors declare no conflict of interest.

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