



Diabetic Bladder Dysfunction: A Review

Luc Wittig, Kevin V. Carlson, J. Matthew Andrews, R. Trafford Crump, and Richard J. Baverstock

Diabetic bladder dysfunction affects almost half of all diabetic patients, making it one of the most common complications of diabetes mellitus. The clinical presentation of diabetic bladder dysfunction can be varied and may be extremely bothersome to patients, negatively impacting their quality of life. Despite this, it remains understudied and under-represented in the medical literature. This review summarizes the current literature on pathophysiology, clinical presentation, urodynamic findings, evaluation, and management. Through this, we hope to provide guidance to clinicians involved with the management of this condition. UROLOGY 123: 1–6, 2019. © 2018 Elsevier Inc.

The incidence of diabetes mellitus has increased worldwide and in North America has reached epidemic proportions. As of 2015, it was estimated that 3.4 million (9.3%) Canadians,¹ and 30.3 million Americans (9.4%)² have a diagnosis of diabetes. Of those affected, about 5%-10% are diagnosed with type I, and approximately 90%-95% have type II.^{1,2} Furthermore, in the United States an estimated 33.9% of adults had prediabetes in 2015 with a large portion of those anticipated to progress to diabetes in the coming years.² The high rates of this chronic disease represent a substantial burden on the health care system, with estimated annual costs in the United States of \$245 billion.²

Diabetes mellitus is a metabolic disorder that results in a state of persistent hyperglycemia. This is most simply mediated by the autoimmune destruction of the insulin producing beta cells (type I diabetes).³ Insulin normally facilitates the transport of glucose into cells of the body, and without it glucose remains in the blood stream for longer and at higher concentrations. A similar result can occur from a combination of genetic and environmental factors which results in increased peripheral insulin resistance.³ In this second case the beta cells of the pancreas work increasingly hard to produce enough insulin to keep blood glucose levels normal (prediabetes). Eventually these cells are unable to maintain this pace and the insulin production is unable to keep blood sugars regulated, causing a relative insulin deficiency and hyperglycemia (type II diabetes).^{3,4} Either case results in chronic hyperglycemia which when untreated has the potential to cause serious impairment of multiple organ systems, including

neuropathy, retinopathy, and nephropathy.⁵ Diabetic autonomic neuropathy can lead to subsequent urological sequelae and profound effects on quality of life (QOL) through erectile dysfunction, retrograde ejaculation, and diabetic bladder dysfunction (DBD).^{6,7}

DBD is a common urological complication afflicting well over 50% of those with longstanding and poorly controlled diabetes.^{6,7} This has been traditionally described as a triad of decreased bladder sensation, increased bladder compliance and capacity, and impaired detrusor contractility.⁷ Currently DBD refers to a diverse group of symptoms that include storage problems such as overactive bladder (OAB) with urgency incontinence, and voiding problems such as impaired bladder emptying, urinary retention, and overflow incontinence.^{7,8} The incidence of DBD is difficult to estimate due to the lack of validated and standardized measures⁷; however, estimates range between 43% and 87% for type I and 25% for type II diabetes.⁴ Despite this high prevalence, and the great effect it has on QOL, DBD remains understudied and under-represented in the medical literature with little to guide practice.⁷

EXPERIMENTAL MODELS AND PATHOPHYSIOLOGY

DBD is difficult to study in humans as the diabetic population is diverse, making standardization difficult. A large proportion of diabetic patients have confounding comorbidities that may influence bladder physiology including obesity, age, benign prostatic hyperplasia (BPH), and pelvic floor disorders, among others. The sparse clinical research focusing on pathophysiology of DBD has largely involved female cohorts in efforts to exclude the effects of BPH. As a result, much of the true underlying pathophysiology of DBD remains unknown. Various rodent models, however, have been developed which provide insight into the mechanisms leading to bladder dysfunction.^{7,9}

From the Cumming School of Medicine, University of Calgary, Calgary, Alberta T2V 1P9, Canada; the Division of Urology, Department of Surgery, Memorial University, St. John's, Nfld, A1C 5S7, Canada; and the Department of Surgery, Cumming School of Medicine, University of Calgary, Calgary, Alberta T2V 1P9, Canada

Address correspondence to: Richard Baverstock, BSc, MD, FRCSC, vesia [Alberta Bladder Centre], University of Calgary, 6601, 7007 14th Street SW, Calgary, Alberta T2V 1P9, Canada. E-mail: richard.baverstock@ahs.ca

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Classically DBD is thought to be a direct result of a two-step process. Initially, DBD presents with compensated bladder hypertrophy and increased contractility due to polyuria. In the second stage progression of DBD is theorized to result from an accumulation of toxic metabolites and involves deterioration in voiding function, detrusor muscle decompensation, and ultimately atonic bladder in end stage patients.¹⁰ This traditional model of DBD has been demonstrated in rodent models where induced diabetic rodents initially had an increase in peak voiding pressures followed by decreased emptying ability.¹⁰ This model also superimposes itself nicely to the classical triad of decreased bladder sensation, increased capacity and decreased contractility. However, some recent studies have demonstrated that a proportion of diabetic patients with a combination of urinary symptoms and urodynamic findings do not fit this rigid stepwise model and instead present with urological findings such as detrusor-sphincter dyssynergia, or loss of the micturition reflex.^{5,11} Recognizing the diverse symptoms associated with DBD, a more modern approach builds off the traditional two-step model, but believes the pathophysiology of DBD is a complex interaction of many cellular changes that occur due to hyperglycemia.¹¹ Such changes can lead to bladder and voiding alterations that largely fit the traditional model but also provide an explanation for varying presentations.

Hyperglycemia, through oxidative stress and other mechanisms, can induce cellular changes within the body.^{4,12} Excess glucose oxidation through the tricarboxylic acid cycle results in the production of electrons which are used in the formation of reactive oxygen species.⁴ This may in part explain the pathophysiology of DBD, specifically through their ability to damage neurons, alter urothelial function, and change smooth muscle architecture.^{4,13}

Normal bladder function requires a complex interaction of multiple neural pathways. In rodent models, oxidative stress interrupts neurotrophins, the proteins that promote the survival of neurons.⁴ This ultimately leads to damage and destruction of nerves fibers, with diabetic rats having decreased nerve density when compared to nondiabetic controls.¹² This has been suggested to explain sensory dysfunction and detrusor underactivity in DBD. Furthermore, the destruction of neurons also occurs to those innervating the urethral and pelvic floor muscles. This results in a decreased ability of the urethral muscles and urinary sphincter to relax, and dyscoordination of the pelvic floor muscles causing voiding obstruction.⁹ Over time these neural changes cause detrusor remodeling and impaired contractility, leading to an increase in postvoid residual urine volume (PVR).

The bladder urothelium, which acts as a diffusion barrier, has important sensory function and may also be a potential victim of diabetic reactive oxidative damage. Multiple studies have been completed demonstrating that urothelial mass increases significantly in diabetic rodents with alteration in the densities of neurotransmitter expression.¹⁴ This potentially represents

another mechanism for the decreased sensory ability of those with DBD.

Although all organs of the body may be subject to the effects of hyperglycemia, the bladder is unique in that it also experiences the sequela of polyuria. Recent studies have demonstrated that simply adding 5% sucrose to the drinking water of rodents to induce diuresis can result in significant bladder changes that parallel those seen in the early stages of DBD of diabetic rodents: an increase in bladder smooth muscle mass and compliance along with an increased functional capacity and voided volume. Studies have shown that bladders taken from diabetic rats initially show an increase of contractility followed by a decrease to below that of nondiabetic controls.¹⁰ This increase in contractility can occur as early as 2 weeks and has been suggested to not only be a result of the hyperglycemia alone, but also the polyuresis resulting from prolonged states of hyperglycemia.¹⁵

Polyuria, however, is not the sole mechanism behind detrusor myogenic changes. When female diabetic rats underwent uretero-vaginal diversion, detrusor myogenic changes were still seen on a cellular level. It was found that hyperglycemia resulted in cellular oxidative stress that can cause alterations in lipid, protein, and DNA which ultimately may lead to organ dysfunction and contribute to DBD.¹⁵ Another study found that hyperglycemia-induced oxidative stress upregulated the proapoptotic pathways in detrusor muscle cells, another possible contributor to bladder atony.¹⁶

PRESENTING SIGNS AND SYMPTOMS

The clinical presentation of DBD is wide-ranging in its makeup and severity. As its pathophysiology predisposes to a slow insidious onset, frequently a large proportion of those affected are unaware of any changes to their bladder even though underlying signs of the condition may be present.^{5,17} Typically, the first manifestation is impaired bladder sensation wherein patients may notice an increase duration of time between voids.^{4,6} However, this change in voiding habits often goes undetected by patients and in those cases the first symptoms may be the development of a Urinary Tract Infection (UTI) secondary to urinary retention.⁴ Others may present with a wide spectrum of urinary complaints related to underlying changes of DBD.⁷

Both storage and voiding Lower Urinary Tract Symptoms (LUTS) are prevalent in those with DBD⁶: Men with diabetes, for example, are up to twice more likely to suffer from LUTS than their nondiabetic peers.¹⁴ One study found that 87% of patients with DBD complained of nocturia, 78% frequency, 62% hesitancy, 52% decreased flow, and 45% sensation of incomplete bladder emptying.¹⁸

Although OAB symptoms are not classical for DBD, there has recently been an increased recognition of this condition within the DBD population. In one study, it was present almost 7.5 times more frequently in the

diabetic population when compared to healthy age-matched controls.¹⁹ OAB may result from polyuria or from the cellular changes described above.²⁰ These patients may complain of any combination of irritative symptoms such as urgency, frequency, nocturia, and urgency incontinence.¹⁹ These OAB symptoms can be severe and impact patients' QOL greatly.²⁰ One study looked at urinary complaints of diabetic women and found that OAB symptoms were the most bothersome (specifically urgency incontinence and nocturia)²¹; as a result, OAB symptoms are often what drives a diabetic patient to seek medical attention.²⁰

Voiding symptoms seen in DBD are due to bladder outlet obstruction and/or detrusor underactivity. Bladder outlet obstruction is theorized to result from impaired ability of the urethra to relax.^{6,9} Those with predominantly obstructive DBD may experience prolonged micturition of large intravesical volumes, straining, recurrent UTIs, poor stream, voiding hesitancy, or overflow incontinence.^{6,7,14} Furthermore, repetitive infections may impose a risk for development of staghorn calculi and other complications.⁶

Urinary incontinence (UI) is consistently demonstrated as one of the most bothersome symptoms of DBD and is a common presenting complaint. UI is present in more than half of patients with diabetes, and diabetic vs nondiabetic women are more than twice as likely to be incontinent.¹⁹⁻²³ Furthermore, it has been shown that UI is associated with glycemic control: In women with moderately controlled diabetes (hemoglobin A1c between 6.5% and 8.5%) each increase of HbA1c of 1% is associated with a 13% increase in any UI and 34% increase in stress incontinence.²²

URODYNAMIC FINDINGS

DBD is a broad diagnosis and the urodynamic findings can be as varied as the presenting symptoms.¹⁸ This is further exacerbated by comorbid factors that influence lower urinary tract function such as age, obesity, and BPH.^{5,18} Urodynamic studies typically highlight the progressive nature of the condition, starting often with storage changes due to an insidious onset of bladder sensation impairment, then development of voiding dysfunction secondary to chronic detrusor overdistention, and eventual decompensation.^{5,18} Findings include delayed first sensation of filling, low end-filling detrusor pressure, and eventual detrusor areflexia. Often, the urodynamic findings of increased PVR and detrusor decompensation can be seen on urodynamics before bothersome urinary symptoms are recognized by patients.²⁴ Other urodynamic findings include urethral dysfunction, loss of detrusor-sphincter coordination, increased bladder outlet resistance or obstruction, and UI. The findings of stress UI is seen in 12.5% of diabetic females undergoing urodynamics and urgency incontinence can be seen in approximately half of DBD patients with detrusor overactivity.^{24,25} Detrusor overactivity occurs in a high proportion of patients with

DBD (25%-55%), with or without coexisting conditions such as bladder outlet obstruction, neurological disease or advanced age.^{6,24} However, detrusor overactivity is often seen in diabetic patients without these concomitant conditions.²⁴ Overall, the predominant urodynamic findings relate to later stage disease (classic "diabetic cystopathy") and include: delayed sensation of filling, increased bladder compliance and capacity, and decreased detrusor contractility with elevated PVR.^{1,5,24}

CLINICAL EVALUATION

The diagnosis of DBD is established through a careful history, physical exam, and urodynamics studies.²⁶ Questions pertaining to LUT function should be asked early and often as the slow onset of DBD often leads to symptoms being overlooked by patients.^{5,17} This underscores the importance of increasing awareness of this condition among all practitioners involved in the care of these patients, including those in primary care, endocrinology, neurology, and urology. Patient reported outcomes (PROs) in the form of validated questionnaires and the use of voiding diaries can be used by any clinician involved in the care of diabetic patients to identify those who may be experiencing symptoms of DBD.^{14,19}

A detailed diabetic history should be taken, as duration and severity of Diabetes Mellitus (DM) may correlate with risk for DBD. One study suggested that the duration of diagnosis of DM greater than 9 years or a hemoglobin A1c value of greater than 7.9% in men, or greater than 8 years or 7% respectively in women, were predictors for a diagnosis of DBD.²⁵ Information regarding any medications or past surgeries that may affect bladder function should also be queried.⁹ Bladder diaries and/or frequency-volume charts are particularly useful in these patients as they can give clues to the onset of DBD as well as the presence of polyuria which can further exacerbate LUTS.¹⁴

On physical examination, sacral cord signs or evidence of other autonomic neuropathies should trigger further investigation and assessment, as these findings have been demonstrated to be associated with DBD.^{5,9,25} An attempt should be made to identify other diseases or conditions that mimic DBD such as BPH, prostate cancer, UTIs, pelvic muscle weakness, or neurological conditions such as spinal cord injuries or cerebrovascular events.^{5,18} Digital rectal examination to assess the prostate and sphincter tone may be considered. In females, gynecological exam to exclude pelvic organ prolapse should also be performed.

Urodynamic evaluation has been reported as the cornerstone of diagnosis and pivotal to individualize treatment for this wide-ranging condition.^{5,7,25} The American Urology Association encourages the use of both PVR testing and urodynamic studies in patients with disturbance of normal bladder function due to diabetes.²⁷ One should strongly consider evaluation of the diabetic patient with known peripheral neuropathy as studies suggest between 75% and 100% of these individuals have some degree of

DBD.^{5,17} It has even been suggested that urodynamic studies should be completed in diabetic patients that have no urinary complaints, as a large proportion of this population has urodynamic findings that may guide management.⁵ Likewise, a correlation between proteinuria associated with diabetic nephropathy and increased PVR volume has been demonstrated.¹⁷ These findings suggest a possible role for urinalysis screening in those who may be at increased risk for DBD. Furthermore, patients with existing diabetic nephropathy should be considered for evaluation of DBD.

MANAGEMENT

Management strategies for DBD are guided by the patient's symptoms, severity, and impact on QOL.⁷ Goals should include the improvement of overall health and optimization of glycemic control, relief of lower urinary tract symptoms, promotion of urinary continence, and preservation of renal function. Generally, treatment strategies for DBD can be categorized into conservative or behavioral, pharmacological, and surgical. PROs and diaries are an excellent method of tracking urinary symptom severity and bother, and can be utilized during repeated assessments to monitor change. Furthermore, urodynamics may be repeated as necessary if warranted by a clinical change or concern.¹⁴

General Measures and Glycemic Control

The first consideration in managing DBD should be glucose control and the management of other factors influencing bladder function. There is evidence suggesting progression of DBD is related to both the duration of hyperglycemia and to blood sugar levels, and individuals with worsening glycemic control are more predisposed to DBD.^{14,21,25} Type II diabetics who are insulin-dependent seem to have worse urologic outcomes compared to those on oral agents alone.²⁸ Lifestyle changes, especially weight loss, may improve outcomes in two ways: First, weight loss through healthy eating and exercise can improve diabetic control and even help in the reversal of insulin dependence in type II DM; second, weight loss may alleviate some urinary symptoms, especially UI.²⁹ Overweight women (BMI 25-45) have been shown to have a 60% reduction in incontinence episodes with 5%-10% weight loss.²⁹

Further optimization of bladder function may be individualized to patient comorbidities. In diabetic men with prostatic enlargement, for example, treatment of their BPH has been shown to improve urinary outcomes.⁶ Optimization of medications should also be considered, and adjustments made where clinically appropriate, including antidiabetic medications themselves. The relatively new class of SGLT2 inhibitors is known to cause glucosuria and increase the risk of polyuria, nocturia, and UTIs; therefore, clinicians and patients must balance the requirement for glycemic control with the patient's urinary symptomatology.³⁰

Overactive Bladder

Frequency and nocturia can be improved by tighter glycemic control to prevent associated polyuria, but also by limiting fluid intake, especially in the evening, and avoiding bladder irritants.⁷ For those that fail conservative management, the next option is pharmacology. First line medication for patients presenting with early signs of DBD and OAB symptoms are anticholinergic drugs and beta-3 agonists.⁶ Multiple studies have demonstrated the ability of anticholinergics to improve bladder symptoms in this patient population when compared to placebo.⁹ Mirabegron, a beta-3 adrenergic agonist, has been shown to relax the detrusor smooth muscle and effectively provide relief from OAB symptoms.⁶

Patients who have attempted pharmacological agents with limited success may be considered for surgical management. Third-line treatments for OAB include intradetrusor injection of onabotulinumtoxinA, percutaneous tibial nerve stimulation, and sacral neuromodulation (SNM). Intradetrusor onabotulinumtoxinA injections and SNM have proven as effective in improving OAB symptoms in patients with diabetes as their nondiabetic control.^{8,31} OnabotulinumtoxinA injections have shown to decrease urinary frequency over a 3-month period as well as significantly improve urinary PROs.³¹ After a successful trial period, SNM proved effective in treating diabetic patients with OAB symptoms, improving frequency in 85% and urgency incontinence in 69% of implanted DBD patients.⁸ In nondiabetic patients, the newer technique of percutaneous tibial nerve stimulation has demonstrated successful results in treating OAB with over 90% of patients experiencing improved clinical and urodynamic outcomes; however, formal studies of diabetic cohorts are lacking.²³

Urinary Incontinence

Patients who experience OAB symptoms or stress incontinence may benefit from pelvic floor exercises such as Kegels,⁹ in addition to weight loss.²⁹ Timed voids every 2-4 hours, decreasing fluid intake, manual compression of the lower abdomen and double voids have also been suggested to decrease the amount of urine in the bladder and promote continence.^{7,14} Female patients with refractory Stress Urinary Incontinence (SUI) may be considered for surgical intervention such as a tension-free vaginal tape, or autologous fascial sling; however, it has been reported that diabetic patients undergoing these surgeries may be at higher risk for treatment failure, dissatisfaction, and postoperative complications.³²⁻³⁴

Impaired Emptying

Patients that present with voiding dysfunction or atonic bladders can attempt voiding techniques including Valsalva maneuvers or manual compression of the abdomen to attempt an increase in abdominal pressures.¹⁴ Double voids or timed voiding may encourage more consistent bladder emptying. When these techniques prove unsatisfactory, clean intermittent self-catheterization (CIC) may

be implemented.^{7,14,25} CIC is often a mainstay of therapy for those patients with bothersome impaired bladder emptying which may manifest as overflow incontinence, recurrent UTIs, nocturia, or OAB. Once mastered or provided by caregivers, patients undertaking CIC may find dramatic improvements in QOL.³⁵ Clinicians must always be wary of possible concomitant conditions such as BPH and if impaired emptying is thought to be a result of prostatic obstruction, introduction of an alpha-blocker and/or 5-alpha reductase inhibitor may be trialed.

Unfortunately for patients suffering from detrusor underactivity of the bladder refractory to conservative therapies, there are no good pharmacological agents. Parasympathomimetic drugs such as bethanechol and carbachol have historically been used in patients with underactive, atonic, or areflexic bladders.^{9,36} Therapeutic use of these agents have been largely anecdotal and there is little in the way of standardized dose, dosing interval, duration of therapy or route of administration.³⁶ By providing additional stimulation of muscarinic receptors of the bladder, it was hoped bladder contractility would be at least partially restored; however, studies have shown that these agents have a negligible clinical benefit.³⁶ Furthermore, parasympathomimetic agents are well recognized for adverse side effects such as flushing, salivation, gastrointestinal distress and even serious events such as circulatory failure or cardiac arrest.³⁶ Ultimately, current evidence suggests that not only is there is little benefit of parasympathomimetic agents, but the adverse side effects of the drugs may outweigh any benefit provided and therefore these agents are rarely used.³⁶

Patients with impaired detrusor contractility who do not benefit from behavioral and pharmacological treatment may be considered for surgical intervention with the aim to improve continence, minimize the risk of infection and preserve renal function.^{7,9} The choice of surgical intervention is often dictated by the nature and severity of symptoms, patient bother, and comorbid conditions. If bladder obstruction is a result of BPH, a transurethral resection of the prostate can be considered.⁶ SNM may be an option for patients complaining of frequency or urgency incontinence and demonstrate atonic detrusor on urodynamics. Over half of diabetic patients with impaired emptying had improved urinary symptoms after 2 years of SNM.⁸ Although promising, SNM has flaws. In order for SNM to be of a benefit, patients must be relatively free of sacral nerve neuropathy and in cases where surgery is completed over a third of devices must eventually be removed do to infection.^{9,37} Ninkovic et al described another surgical option for bladder acontractility in which skeletal muscle is used for detrusor replacement.³⁷ In this procedure, a portion of the latissimus dorsi and associated neurovascular bundle is harvested and transferred to wrap around the bladder and secured to the pelvic fascia. The inferior epigastric vessels are used for vascular supply and the innervation is supplied by the lowermost segmental motor neuron supplying the rectus abdominus. Postsurgery the vast majority of patients are able to spontaneously void by contracting their lower abdominal musculature; however, little is known about this procedure in the diabetic population.

FUTURE DIRECTIONS

DBD represents a major economic burden to the health care system and a significant source of patient morbidity. Despite being the most common complication of diabetes, it is under-represented in research and work to fully elucidate the precise pathophysiology driving DBD is needed. Recent research has shown beneficial applications of antioxidants to prevent cellular damage of oxidative stress and ultimately prevent neuropathy in diabetic rodents.³⁸ Another novel treatment for DBD developed in rodent models is the injection of ex-vivo cultured smooth muscle cells into diabetic rat bladders to produce an increase in contractility and a reduction in residual urine.³⁹ Kim et al undertook studies looking at the use of stem cells in the treatment of bladder dysfunction in animal models.⁴⁰ Although incompletely understood, improvement in urodynamic findings has been demonstrated with the transplantation of stem cells into the bladder for both bladder overactivity and underactivity in rodent models. Last, as the development of skeletal muscle to detrusor transfers in spinal cord injuries is further developed there is hope that this technology and procedure can be applied to the diabetic population with success.

Clinical research and quality improvement opportunities abound in the management of DBD. Awareness of the changes of DBD is not well known to nonurologist practitioners and even to those urologists whose practice does not focus in voiding dysfunction. Development of review articles and other Continuing Medical Education (CME) materials to highlight the interaction of diabetes and LUTS are important to educate all practitioners. Treatment among specialists is often disjointed and largely the responsibility of urologists who frequently do not see these patients until the condition is quite advanced. Ideally, patients who initially present with urinary complaints should be encouraged toward tighter glycemic control by their primary care provider or diabetic specialist, as this has been shown to slow the progression of DBD.^{22,24} Furthermore, the presence of DBD should trigger referral to specialty care as it is one of the most common and earliest diabetic complications.^{6,7} Further research into outcomes based on this proposed early recognition and referral is warranted, and guideline development is needed.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.urology.2018.10.010](https://doi.org/10.1016/j.urology.2018.10.010).

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