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Bladder Dysfunction in Patients with Diabetes

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Abstract With diabetes mellitus (DM) reaching epidemic proportions, the identification of voiding dysfunction as a common and burdensome complication of this disease is critical. Research into diabetic voiding dysfunction significantly lags behind other complications of DM, such as retinopathy and nephropathy. Recent studies have revealed that DM predisposes patients to a wide range of lower urinary tract dysfunction, from the classic diabetic cystopathy of incomplete emptying to urgency incontinence. In this review, we discuss the current concepts of diabetic voiding dysfunction with a critical analysis of the available evidence.

Keywords Diabetes mellitus · Diabetic cystopathy · Voiding dysfunction · Overactive bladder · Urinary incontinence · Comorbidities · Quality of life

Introduction

According to the American Diabetes Association, there are currently 25.8 million adults and children with diabetes mellitus (DM) in the United States. Of this population, 7 million are currently undiagnosed and there are an additional 79 million with prediabetes [1]. These numbers represent the epidemic that DM has become. Diabetic voiding dysfunction (DVD) is reported to be a far more common complication of DM than the widely recognized complications such as neuropathy and nephropathy. DVD has been reported in 80% of individuals with DM. On the contrary, neuropathy and nephropathy have been reported to affect 60% and 50% of diabetic patients, respectively [2]. However, little is known about the natural history of the disease and the onset of urological symptoms. This paucity of knowledge has been a barrier to developing newer and effective prevention and treatment options for this population.

The lower urinary tract dysfunction found in these patients covers a broad spectrum from diabetic cystopathy to overactive bladder (OAB) and incontinence. This paper presents a critical review of the current concepts of DVD, including animal models for research, possible pathophysiology of urinary tract dysfunction, the typical presenting signs and symptoms, and therapeutic options.

Animal Models

The progression and nature of DVD in humans cannot be easily studied because access to affected organs and tissues for experimental investigations is not readily available. Additionally, the natural history of DM and its urological complications spans over decades and it is often difficult to conduct studies over such prolonged periods. Hence, a creditable animal model is solely required. Furthermore, the natural history of the disease is greatly compressed in animals given their lifespan, and this allows faster data collection and lowers costs.

Animal models comprise both small (eg, rodent) and large (eg, swine, rabbit, and monkey) models. Although larger animals have closer phenotypic resemblance to humans, the interval between DM onset and development of complications is prolonged, and costs associated with animal husbandry for large sample sizes are prohibitively expensive. Hence, rodent models have gained increasing attention.

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Temporal Hypothesis

DVD can present as a wide spectrum of symptoms, including diabetic bladder dysfunction (DBD), erectile dysfunction, and urinary tract infections (UTIs). Past studies have shown that the morphological and functional manifestations of DVD are time-dependent; this has been true in humans and in type 1 DM rat models. The temporal hypothesis classifies DVD manifestations into early and late phases. Early phase manifests as filling problems, comprising OAB symptoms and hypercontractile detrusor [3]. The last phase manifests as voiding problems, comprising urinary retention and acontractile detrusor [4]. While this is discussed and represented in animal models, evidence in human clinical studies to support this theory is lacking.

Type 1 Diabetes Mellitus Animal Models

Chemical destruction of pancreatic β-cells leading to hyperglycemia is a well-accepted technique to induce type 1 DM in animal models [5•]. Streptozotocin and alloxan are widely used to induce type 1 DM in rodent models. Streptozotocin is an alkylating agent that interferes with glucose transport. Injecting multiple small doses of streptozotocin causes permanent direct destruction of pancreatic β-cells, leading to hypoinsulinemia [5•].

Genetically induced type 1 DM mouse models also have been used widely. The rodents develop type 1 DM either due to autoimmunity or by selective inbreeding. A few well-known models are the nonobese diabetic mouse, the Akita mouse, and the diabetes-prone BioBreeding rat [6]. While the latter two models are examples of genetic mutations, the first model results from severe autoimmunity.

Type 2 Diabetes Mellitus Animal Models

Taking into consideration the multifactorial origin of type 2 DM, several monogenic and polygenic mouse models have been successfully developed. In general, polygenic models are thought to be more representative of the human pathogenic pathways and clinical manifestations [5•]. Monogenic models result from leptin deficiency or receptor mutations, the final result being uncontrolled appetite and obesity leading to type 2 DM. Polygenic models involve combining independent DM risk conferring traits from two unrelated parental strains (New Zealand obese [NZO]/H1Lt and NON/Leiter [Lt] mice).

The spontaneously diabetic Torii rat (Torii Pharmaceutical Co., Chiba, Japan) was developed by inbreeding Sprague–Dawley rats. Male rats were found to develop type 2 DM spontaneously without obesity at 20 weeks [7]. Similarly, selective inbreeding of Wistar rats resulted in the Goto-Kakizaki rats. This model had very close resemblance to type 2 DM in humans. Additionally, the rats developed DM as early as 4 weeks [8].

Pathophysiology

The pathophysiology of bladder dysfunction in diabetic patients has been found to be multifactorial, with neuronal dysfunction, smooth muscle dysfunction, and the urothelium contributing to the widespread signs and symptoms seen in these patients.

Neuronal Dysfunction

Neuronal dysfunction leading to classic diabetic cystopathy with impaired sensation, decreased contractility, and impaired emptying has been easier to explain than neuronal dysfunction leading to OAB. Altered metabolism of glucose, ischemia, superoxide-induced free-radical formation, and impaired axonal transport are proposed hypotheses for the peripheral nerve damage seen in diabetic patients [9]. Axonal degeneration as well as segmental demyelination can cause impaired conduction of the visceral afferent fibers from the bladder [10]. This was proven clinically when Lee et al. [11] found decreased sensory response of the Aδ and C fibers of the bladder when measuring intravesical current perception threshold in diabetic patients. Defects in axonal transport, specifically nerve growth factor (NGF), also have been proposed as mechanisms of diabetic neuropathy and cystopathy. In diabetes-induced rats, NGF levels in the bladder, L6–S1 dorsal root ganglia, and sciatic nerve were significantly decreased after streptozotocin injection [12, 13]. The decrease in NGF levels was associated with increased bladder capacity and postvoid residual (PVR). Gene therapy using herpes simplex virus vectors expressing NGF injected into the bladder wall of streptozotocin-induced diabetic rats was able to partially reverse these findings as well as increase NGF levels when compared to controls [14].

While these findings implicate neuronal dysfunction as an important mechanism in diabetic cystopathy, they fail to explain the common clinical findings of OAB and urgency incontinence. As a possible explanation for OAB in diabetic patients, Yamaguchi et al. [15] proposed that these symptoms are secondary to diabetic vasculopathy leading to multiple cerebral infarcts. This study found a trend toward increased urinary frequency and nocturia in diabetic patients with abnormal brain magnetic resonance imaging (MRI) scans, but failed to reach statistical significance.

The reality that the pathophysiology of diabetic cystopathy has been more clearly defined than that of OAB is likely due to the fact that animal models more commonly replicate

diabetic cystopathy rather than DBD in the form of OAB. On the other hand, clinical scenarios have coexisting conditions that may contribute to the OAB symptoms (eg, cerebrovascular accident and DM or benign prostatic hypertrophy and DM) discussed later in this article.

Detrusor Smooth Muscle Dysfunction

Although multiple studies have proven detrusor smooth muscle dysfunction in diabetic animal models, there is not a consensus on the mechanism, time course, or implication of diabetes-related changes in detrusor smooth muscle cell function. Pharmacological studies on isolated bladder strips from differing animal models have led to much of the confusion.

Increased responsiveness of these bladder strips to externally applied muscarinic agonists as well as increased muscarinic receptor density has been shown by some, while others have shown a decrease or no change in the muscarinic component [16]. Increased responsiveness to electrical field stimulation has been repeatedly seen and theorized to be secondary to changes in membrane composition, increased neurotransmitter release, increased calcium channel activity, and increased calcium sensitivity [17]. An increase in purinergic receptors and purinergic transmitters has been seen in a diabetic rabbit model. Furthermore, purinergic receptor expression was found to be inhibited by insulin [18]. Neuronal nitric oxide (NO) synthase was found to be upregulated in the smooth muscle of diabetic rats and is proposed to be an early change in DM and a possible cause of bladder dysfunction [19].

Urethral dysfunction in diabetes has received less attention than bladder dysfunction, but has shown that it has significant implications in diabetic cystopathy. Diabetic urethropathy is characterized by impaired relaxation of the urethral striated and smooth muscle, decreased NO responsiveness, and increased responsiveness to α_1-adrenergic agonists [20, 21]. This likely acts as a cohort with bladder dysfunction to decrease voiding efficiency and increase PVR.

Urothelial Dysfunction

It has become increasingly apparent that the urothelium is not just a passive barrier of the bladder, but rather is actively involved in bladder function and dysfunction. The urothelium directly communicates with suburothelial afferents through the release of NO, adenosine triphosphate (ATP), and prostaglandins. The urothelium also has its own receptors such as VR-1, a vanilloid receptor that is potentiated by ATP [17]. Diabetic rat models have shown that the urothelium thickness increases in a time-dependent manner. Endogenous prostaglandins E2 and $F_{2\alpha}$ increased in diabetic rats while $F_{3\alpha}$ decreased when expressed as a fraction of tissue weight. The release of these prostaglandins sensitizes sensory nerves and has the potential to contribute to OAB symptoms seen in diabetic patients [17, 22]. These findings show that the urothelium has a potential role in OAB symptoms of diabetic patients, but to what degree and in what context is still unclear.

Clinical Signs and Symptoms of Diabetic Voiding Dysfunction

It has become increasingly evident that diabetic patients have significant bother from both emptying and storage symptoms. These symptoms are not mutually exclusive, and patients with poor emptying from diabetic cystopathy also may have significant bother from OAB. Kaplan et al. [23] found that while the classic symptoms of hesitancy (62%), reduced stream (52%), and incomplete emptying (45%) were prevalent, the symptoms of nocturia (87%) and urinary frequency (78%) were the most common in their cohort of diabetic patients. While a time-dependent progression from OAB to emptying failure has not been shown in clinical cohorts, time with diabetes and peripheral neuropathy have correlated with decreased emptying efficiency as well as the incidence of urinary incontinence [24, 25].

Early signs and symptoms of failure to empty often are overlooked by the patient due to the insidious onset and often require directed questioning. Lee et al. [25] highlighted the symptoms of DBD when they used the American Urological Association Symptom Index (AUA-SI) to compare bothersome urinary symptoms in diabetic versus nondiabetic women. They showed that diabetic patients had significantly higher AUA-SI scores for weak urinary streams, which was corroborated with a lower maximal flow rate (19.4 vs 25.9 mL/s), decreased voided volume (220 vs 280 mL), and increased incidence of PVR over 100 mL (13.9% vs 1.8%). Patients categorized as having DBD (PVR>100 mL, bladder voiding efficiency <75%, or bladder capacity >500 mL) were found to have significantly higher storage and emptying scores, as well as lower quality of life (QOL), than diabetic patients without DBD as measured by the AUS-SI [26].

OAB symptoms also have proven to have significant detrimental impact on QOL. A variety of standardized questionnaires (eg, AUA-SI, International Consultation on Incontinence Modular Questionnaire-Female Lower Urinary Tract Symptoms [ICIQ-FLUTS], and Kings Health Questionnaire) have been consistent in showing that nocturia and number of incontinence episodes have a significant impact on QOL [26, 27]. These findings were

not associated with increased urine production when compared with bladder diary measurements [27]. This leads one to believe that the pathophysiology is more likely in line with OAB theories than the diuretic effect of DM.

Early retrospective reports demonstrated that DM increased the incidence of urinary incontinence after stroke [28]. This has been followed-up with cross-sectional analyses of longitudinal studies such as the Nurses' Health Study Cohort (NHS) and the National Health and Nutrition Examination Survey (NHANES) [24, 29]. The NHS showed that both the prevalence and incidence of urinary incontinence were increased in women with DM. The risk of incontinence increased with increasing duration of DM. Furthermore, the severity of incontinence also was increased in diabetic patients. Patients with DM had a relative risk (RR) of 1.97 for severe incontinence (defined as enough leakage to wet the outer clothing) [24]. In contrast to the NHS, the NHANES was able to look at the incidence of incontinence by type (stress and urgency). The NHANES also added intriguing information by including patients with impaired fasting glucose (IFG) as well as type 2 DM. Brown et al. [29] reported the finding that the prevalence of weekly incontinence was similar among women with IFG and DM (33.4% and 35.4%), but significantly higher than women with a normal fasting glucose (16.8%). This finding was true when looking individually at both stress and urgency incontinence. Among women with incontinence, both diabetic and prediabetic women were more likely to report being bothered by their incontinence and felt that incontinence affected their daily activities significantly more than nondiabetic women. This concurs with the finding by Fayyad et al. [27] that number of incontinence episodes correlated with the finding of bothersome lower urinary tract symptoms (LUTS). For diabetic women, a history of foot ulcer and macroalbuminuria were associated risk factors for urgency incontinence. For women with IFG, the presence of macroalbuminuria significantly increased the presence of both stress and urgency incontinence [29].

From these reports we can see that diabetic patients can present with a wide range of signs and symptoms. Which patients are prone to emptying, storage, or a combination of symptoms has not been elucidated and significant work remains to be done.

Urodynamic Findings in Diabetic Bladder Dysfunction

Traditionally, diabetic cystopathy has been described as impaired bladder sensation, increased bladder capacity, decreased detrusor contractility and an increased PVR volume [30]. However, these are not the only manifestations or urodynamic (UDS) findings in patients with diabetic cystopathy. Kaplan et al. [23] reported that detrusor overactivity (48%) was the most common UDS finding, followed by impaired detrusor contractility (30%) and impaired compliance (15%) [23].

Based on the results from several studies, detrusor overactivity is the most predominant UDS finding in patients with DM. Multiple cerebral infarcts due to cerebral vasculopathy has been proposed as the probable cause. Yamaguchi et al. [15] demonstrated that the frequency of multiple cerebral infarcts in DM patients with detrusor overactivity was 76.5% on magnetic resonance imaging (MRI). In a study by Ho et al. [31], diabetic patients with OAB symptoms were more likely to have higher voiding symptom scores, lower peak flow rate, elevated PVR volume, and higher incidence of bladder outlet obstruction (BOO [26.5% in the OAB group vs 6.7% in the non-OAB group]). Impaired voiding function may be explained by the higher incidence of BOO. Impaired urethral relaxation during bladder contractions has been reported in animal models and supports the higher incidence of BOO in patients with DM [32]. Additionally, in a study of 173 diabetic patients (78 men and 95 women), 31.7% were found to have detrusor-external sphincter dyssynergia (DESD), which presents as BOO [33]. The presence of BOO has been associated with the development of OAB symptoms. BOO can increase PVR volumes and exaggerates OAB symptoms [15].

In conclusion, there is no single set of UDS findings that applies to all patients with DM. The increased incidence of OAB and BOO carries great impetus in treating these patients. Early diagnosis and treatment of BOO is crucial because the relief not only improves voiding function, but also can prevent the development of OAB in this population. This broad spectrum of findings supports the notion that patients with DVD should undergo UDS testing.

Benign Prostatic Hyperplasia and Diabetes Mellitus

Not only do benign prostatic hyperplasia (BPH) and diabetes have significant overlap in voiding dysfunction symptoms, but evidence also exists that diabetes promotes the disease process of BPH. BPH is believed to cause LUTS through a dynamic component of increased smooth muscle tone mediated by α_1-adrenergic receptors as well as a static component of BOO due to the mass of the prostate. Diabetes is thought to increase the sympathetic tone of the prostate through high insulin level, which increases sympathetic nerve activity as well as cytosolic-free calcium in smooth muscle cells and neural tissue [34, 35]. The binding of insulin to insulin growth factor (IGF) receptors, as well as increasing the transcription of genes involved in sex hormone metabolism, are thought to promote prostate growth [34].

The bothersome storage symptoms of urinary frequency and urgency as well as the emptying symptoms of reduced urinary stream and incomplete bladder emptying are found in both patients with BPH and diabetic patients. The significant overlap of these symptoms supports the idea to refrain from categorizing patients into a single syndrome. Kaplan et al. [23] exemplified this by showing that 57% of diabetic men with persistent voiding symptoms had BOO on UDS.

In a large cohort of patients with clinically diagnosed BPH, patients with diabetes (13%) had a greater International Prostate Symptom Score at baseline as well as a lower flow rate [36]. There is also evidence that diabetes and IFG are associated with increased prostate volume size [37]. This has been challenged by Burke et al. [38], who found no difference in prostate growth when diabetic patients were compared to control patients.

There is also debate regarding the risk of BPH surgery among diabetic patients. Increased serum levels of IGF-1 and IGF-3 were associated with an increased risk of surgery [39], which is in contrast to the study by Sidney et al. [40], which found a decreased risk of surgically treated BPH in patients with high blood glucose.

While much of the literature supports an association between DM and LUTS, debate still exists regarding the association of DM and BPH. This is likely due to the clinical overlap of BPH and OAB, as well as failure to adequately differentiate these patients.

Diabetes Mellitus and Urinary Tract Infections

Multiple studies have shown that individuals with diabetes have an increased RR (1.21–2.22) of UTI compared to those without diabetes [41–44]. Recurrent UTIs not only have an independent morbidity, but also often exacerbate the patient's LUTS and incontinence. Proposed mechanisms for the increased incidence of UTIs in diabetic patients include glucosuria promoting bacterial growth, impaired host immune function, and incomplete bladder emptying [10, 41, 43, 44]. As reviewed by Chen et al. [41], current research has not been able to show a correlation with either serum or urine glucose level when using HgA_{1c} (glycated hemoglobin) as a marker. Rather, it has been shown that UTI risk increases with disease duration and severity of disease. Impaired host granulocyte function, as measured by decreased urinary interleukin (IL)-6 and IL-8 in diabetic patients with asymptomatic bacteriuria, is a possible contributor to these infections. It also has been shown that *Escherichia coli* expressing type 1 fimbriae have increased adherence to the urothelium of diabetic patients [10, 41].

Although PVR volumes are increased in diabetic patients, Boyko et al. [42], in their multivariate analysis, found that this was not a significant variable causing increased UTI risk. This same study showed that although *E. coli* was the most common causative organism for UTIs in both diabetic and nondiabetic patients, first episodes of asymptomatic bacteruria (ASB) more often were caused by *Klebsiella* and *Enterococcus* in women with diabetes. Routine screening and treatment of ASB has been shown in a randomized controlled trial to not reduce the risk of symptomatic UTIs [45]. This information adds to the knowledge gap in this area and supports the need for increased translational research to further understand the mechanism between diabetes, ASB, and UTIs.

Clinical Evaluation and Treatment

Initial Evaluation

Despite the increased incidence of LUTS in diabetic patients, they have been commonly overlooked by health care providers. Screening patients for neuropathy and nephropathy has carried great impetus. On the contrary, LUTS in patients with DM have been commonly attributed to polyuria and are not given due attention. This approach delays treatment and permits disease progression.

All patients should be screened with a thorough history and physical exam. Common presenting symptoms are nocturia, frequency, urgency, incomplete bladder emptying, poor stream, recurrent UTIs, and stress and urgency incontinence. All patients should be evaluated with validated questionnaires about urinary symptoms and bladder diaries to assess fluid intake and output, frequency, and nocturia. Emphasis should be given to medical and surgical history, concomitant medications that can affect bladder function, and glycemic control.

Urine analysis, serum glucose, glycosylated hemoglobin, urea, creatinine, and screening for end organ damage should be performed on all patients. Given the increased incidence of OAB and BOO in diabetic patients, UDS studies may be required for a complete evaluation of the lower urinary tract [31].

Management Strategies

Treatment of LUTS in diabetic patients does not differ from treatment in those without DM. Management depends on the severity of symptoms, degree of bother, and impact on QOL.

Glycemic Control

In the initial stages, glycemic control can be achieved by diet, exercise, and weight reduction. Patients unable to

maintain glycemic control with conservative management will require addition of oral hypoglycemic agents, insulin, or both. Van Den Eeden et al. [46] reported their findings on the effect of glycemic control on LUTS in 591 men with type 1 diabetes. Despite intensive glycemic control, they did not note any improvement in the severity of LUTS in their cohort. Glycemic control prevents end organ damage, but has not been proved to improve or limit the progression of LUTS in diabetic patients.

Conservative Management

Timed voiding and double voiding has been shown to be useful in patients with decreased bladder sensation and elevated PVR volumes. Adhering to a schedule ensures adequate bladder emptying and may decrease urinary frequency and nocturia [10]. In patients with significant impaired detrusor contractility and impaired voiding, clean intermittent catheterization (CIC) every 4 to 6 h is warranted to prevent worsening of renal function [10].

Medical Management

Treatment of OAB and LUTS in diabetic patients should differ little from patients without DM. With the predominance of urgency, frequency, and nocturia, the use of antimuscarinic medications may be beneficial in this population. Increased muscarinic receptor expression has been seen in streptozotocin-induced rat models, and this provides supporting evidence for the use of antimuscarinic medication to alleviate voiding symptoms in diabetic patients [16]. However, clinical data to support its use is scarce.

Lack of urethral relaxation and presence of DESD during voiding has been reported in diabetic patients. This results in the exacerbation of BOO. Additionally, functional sphincter dyssynergia brought on by Valsalva maneuver to overcome inadequate detrusor contractility also should be taken into consideration when evaluating BOO in diabetic patients. The use of α_1-adrenergic antagonist has been shown to improve voiding in both animal and human models [21]. Early recognition of BOO and initiating treatment prevents worsening of symptoms and the onset of OAB in this population.

Surgical Management

Sacral neuromodulation has been a promising therapy in patients with voiding difficulties, refractory OAB symptoms, and nonobstructive retention. Daniels et al. [47•] compared the efficacy of sacral neuromodulation in diabetic patients and age-matched control patients. No significant difference was noted in successful conversion rates, long-term success rates, and satisfaction with symptom improvement between the two groups. A worldwide clinical trial reported 68%, 56%, and 71% improvement in symptoms in urge incontinence, urgency/frequency, and urinary retention after a 5-year follow-up in diabetic patients [48]. Diabetic patients were noted to have increased risk of device explantation secondary to infection compared to nondiabetic control patients [47•].

Currently, there are no prospective trials reporting the use of botulinum toxin A in the treatment of refractory OAB symptoms in diabetic patients. The risk of CIC after the injection in this population is yet to be evaluated. However, in our practice, diabetic patients with refractory OAB have shown significant improvement in symptoms after intradetrusor injections of botulinum toxin-A.

Scope for Future Research

Animal studies have shown decreased NGF in the bladder and at the L6 dorsal root ganglion in diabetic rats. Sasaki et al. [14] demonstrated that bladder wall injections of replication-defective herpes simplex virus–1 vectors expressing β-NGF restored the decreased tissue NGF levels in the bladder and L6 dorsal root ganglion. They reported that restoration of NGF levels significantly improved voiding function in rats [14]. Similarly, intraperitoneal injection of vitamin E has been shown to decrease apoptosis of uroepithelial cells in diabetic rats [49]. Injection of N-hexacosanol has been shown to have a beneficial effect on detrusor hyperactivity by decreasing the overexpression of M2 and M3 receptor messenger RNAs in diabetic rats [50]. Translational research studies in humans are yet to be performed for the above-mentioned scenarios.

Conclusions

Given the high incidence of DM in the general population, clinicians must be aware of the association of lower urinary tract dysfunction in these patients. Despite evidence suggesting an increased risk of LUTS impacting QOL, many patients and physicians fail to appropriately address and treat this known complication with the same vigor they would treat other complications of DM. Although many patients will present with the classic symptoms of diabetic cystopathy, it is now clear that a significant number will have OAB and possible urinary incontinence. The varied presentation of these patients emphasizes the importance of UDS testing to determine all aspects of bladder dysfunction. Despite a scarcity of data, this article presents a critical review of the available treatment options for these patients to aide physicians in appropriate interventions. Future research efforts to identify the pathophysiology of the

disease as well as preventative measure and interventions will be greatly appreciated.

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