HHS Public Access

Author manuscript

Curr Bladder Dysfunct Rep. Author manuscript; available in PMC 2019 March 19.

Published in final edited form as:

Curr Bladder Dysfunct Rep. 2014 December ; 9(4): 261–267. doi:10.1007/s11884-014-0255-6.

Is the Diabetic Bladder a Neurogenic Bladder? Evidence from the Literature

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Abstract

Diabetes can often cause LUTS. This has been called diabetic cystopathy by many authors, but no concise grouping of symptoms for this condition has been agreed upon. The etiology of diabetic cystopathy remains unknown, but evidence from the literature strongly suggests a neurologic etiology as the primary factor, with other factors such as polyuria, damage to muscle from oxidative stress, and urothelial factors possibly contributing. Once a standard definition for diabetic cystopathy can be agreed upon, prospective, longitudinal studies will play a key role in the generation of hypotheses for the causes of diabetic cystopathy. Animal models will help test these hypotheses and possibly provide strategies for prevention.

Introduction

Diabetes is very prevalent worldwide, with an estimated 382 million people carrying the diagnosis in 2013. This number is projected to increase to 592 million by 2035 [1]. Such numbers make this one of the most significant health issues in the world. Diabetes is associated with significant healthcare cost, patient disability, and even premature death. Those suffering from diabetes often have significant lower urinary tract symptoms (LUTS), including incontinence. This has been estimated to affect up to 80–93% of those with diabetes [2,3].

DM2 has been associated with incontinence, but not DM1. Danforth and colleagues using data from over 71,000 of the 116,671 women enrolled in the Nurse's Health Study I and II noted a weak but increased prevalence of urinary incontinence affecting women with DM2, even when controlled for other factors known to contribute to incontinence (OR 1.2, 95% Confidence Interval 1–1.3). This appeared to be urge urinary incontinence, with no increased association for stress or mixed incontinence [4]. The distinction between urge incontinence and stress incontinence was made by self-report, using mail-in questionnaires. Incontinence was defined as one or more leakage episodes in a 1 week period.

LUTS in the diabetic has been termed **diabetic cystopathy** by some, but what does this term really mean? Although diabetic cystopathy is common it is poorly understood. The term was used by Frimodt-Moller in the 1970's to describe a condition in which diabetics suffer

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voiding dysfunction secondary to autonomic neuropathy [5]. It is presumed to begin with impaired bladder sensation and then progresses to impaired contractility and urinary retention[6]. Diabetic cystopathy is seen in 43–87% of insulin dependent diabetics, and 25% of those on oral hypoglycemic agents [3●●,7], but very little is known about the development and progression of this syndrome over time. The only prospective population based study described a 93% incidence of LUTS with 88% having positive findings on urodynamic studies [3]. The majority of the reports in the literature are prevalence studies, and do not inform the medical community on the course of cystopathy over time, potential benefits of early urologic intervention, or even if early detection of diabetic cystopathy is possible.

The impact of DM1 on the bladder compared with DM2 is controversial. Contrary to the findings of Danforth mentioned earlier, urinary incontinence can be 50–200% more likely in women with DM2 [8]. Diabetes has also been associated with moderate to severe Lower Urinary Tract Symptoms (LUTS) using the validated American Urological Association (AUA) symptom index score (34.6% vs. 21% of women with diabetes vs. controls) [9]. Diabetic cystopathy may contribute to some life threatening complications, such as renal impairment. One prospective diabetes registry in Hong Kong noted 19.7% incidence of chronic kidney disease over a median follow-up period of 7.2 years [10]. Another noted impaired detrusor contractility in 918 of 1,640 consecutive diabetic women from China [3●●]. There is a high correlation between diabetic cystopathy and other end-organ damage, such as peripheral neuropathy [11,12]. There is also evidence that histologic changes accompany diabetic cystopathy in the chemically induced rabbit model [13]. The primary method to diagnose diabetic cystopathy involves combining clinical symptoms (LUTS, urinary incontinence, and urinary retention) with bladder pressure measurements from a urodynamic study. In summary, the literature clearly demonstrates that diabetes is associated with significant urologic complications, but unfortunately there is no standardized definition for diabetic cystopathy, nor any methods to detect these changes at an early stage or even how to follow progression over time. There is a relative paucity of clinical data in the literature on this topic and only a few urologic animal models for the study of diabetic cystopathy. Technology to measure bladder pressure in-vivo, over long periods of time may also be beneficial. The role neuropathy plays in this process will be explored in the following paragraphs.

Clinical Reports Describing Diabetic Cystopathy

One time honored method to understand human disease is to take a cohort of patients with the disease and phenotype them. Once the phenotype is understood, animal models can be helpful to elucidate the mechanism and test possible therapeutic options. The main tools available to phenotype patients with diabetic cystopathy are the bladder diary, validated questionnaires describing LUTS, and urodynamic studies.

Although much has been published on diabetes, relatively few clinical reports have been published on diabetic cystopathy. There is, in fact, no standardized definition for diabetic cystopathy, leading some authors to call for one [14]. One agreed-upon feature is elevated post void residual volumes.

With this in mind, women with diabetes have been proven to have **lower flow rates** and **higher post void residual volumes** when compared to age-matched, parity-matched, and BMI-matched women without diabetes. A group of investigators in Taiwan demonstrated this in 194 women with DM1 and DM2 compared with 162 women without DM. Uroflow and AUA symptom index score were the primary endpoints. Post void residual was greater than 100cc in 13.9% of diabetic patients and only 1.8% of controls. Mean maximum flow rate was 19.4cc/sec in diabetics compared to 25.9cc/sec in controls ($p<0.001$). **Emptying efficiency** (voided volume compared to post void residual) **was significantly worse in women with a diagnosis of peripheral neuropathy** or duration of diabetes >10 years using multiple regression modeling. Age also worsened emptying efficiency [9].

Poor sensation of filling is another hallmark of diabetic cystopathy, and may contribute to the findings in the previous study. One way to determine this is to measure sensation during the urodynamic study. Investigators from Taiwan combined urodynamic studies with an interesting electrical stimulation technique.

Bladder sensory function was studied in 86 women with DM2 at a diabetes clinic in Taiwan by applying current to a catheter during urodynamic studies, with a frequency of 250 Hz intended to elicit a sensory response in A delta fibers and a frequency of 5 Hz intended to elicit a response in C fibers. 38.4% of these women demonstrated normal urodynamic studies. These were used as a control group. 34.9% demonstrated detrusor underactivity, defined by Schafer and ICS nomograms. The **investigators demonstrated impaired current perception thresholds for both A delta and C fibers between the two groups correlated with lower voided volume, lower Qmax, and higher PVR**. It is interesting to note that higher current perception thresholds for both A delta and C fibers were not associated with elevated first sensation of filling, as one might have expected. This is the first study to link impaired A delta and C fiber sensory function in the bladder with urodynamically proven detrusor underactivity [15●].

Others investigated motor nerve conduction velocity and found that abnormal motor nerve conduction velocity is associated with urodynamic proven voiding dysfunction, but symptoms may not be [16]. In that investigation, *sensory* nerve conduction velocity was assessed in 29 patients using the sural nerve. *Motor* nerve conduction velocity was assessed using the peroneal nerve. LUTS were assessed by administering the International Prostate Symptom Score (IPSS). Voiding dysfunction was defined by delayed first desire to void >300cc and maximum bladder capacity of >500cc. They concluded that **impaired nerve conduction velocity is highly correlated with delayed first desire to void and elevated capacity in diabetics**, but LUTS (using IPSS) were not correlated with these urodynamic findings [16]. This is significant in that it suggests peripheral nerve conduction velocity testing may predict voiding dysfunction without urodynamic testing. Furthermore, impaired nerve conduction velocity may come before LUTS are noticed by the patient, possibly serving as an early predictor of diabetic cystopathy. Investigators from Japan sought to establish a connection between thermoreceptors in the bladder and urodynamic findings by filling the bladders of 32 subjects with ice water after urodynamic evaluation.

Although more patients in the diabetic cystopathy group reported impaired sensation of filling (25% vs. 12.5%), they found no statistically significant correlation between inability to feel the ice water and peripheral neuropathy. Not all patients with diabetic cystopathy demonstrated impaired sensation of filling, but among those that did, only 36.4% also had impaired ice water sensation [17]. This pilot study suggests that **thermoreceptors may not be linked to diabetic cystopathy**.

Just as bladder sensory thresholds and nerve conduction velocity can predict some elements of diabetic cystopathy, evidence of peripheral neuropathy in other organs can predict diabetic cystopathy. As early as the '80's Frimodt-Moller noted diabetic cystopathy is highly correlated with peripheral neuropathy (75–100%) as well as duration of diabetes (the prevalence of diabetic cystopathy in diabetics diagnosed for 10 years or longer was 2–4 per 1000) [7]. Kebapci and colleagues investigated 54 men and women in Turkey with DM2 having urodynamic findings. They defined **diabetic** cystopathy as impaired **bladder** sensation, increased post-void residual urine (PVR), increased **bladder** capacity, and decreased **bladder** contractility and found that evidence of peripheral neuropathy was an important predictor of diabetic cystopathy. 50% of men and 43.7% of women exhibited diabetic cystopathy by their criteria. They also found age, duration of diabetes since diagnosis, and Hgb A1c predicted diabetic cystopathy, but the actual threshold varied in men compared to women. The threshold for age in men compared to women was >64 vs. >56. For duration of diabetes it was >9y for men vs. >8y for women. For Hgb A1c it was >7.9% vs. >7.0% [6]. Similar to these findings, Kaplan, Blaivas and colleagues noted a 26% incidence of diabetic neuropathy in 182 consecutive urodynamic studies on diabetic patients [18].

Van Poppel found evidence of decreased neurologic activity at the cellular level by performing neuropathological examination on bladder biopsies of 14 patients with severe insulin-dependent adult-onset diabetes. They compared acetylcholinesterase levels and S100 staining of those 14 patients with 38 control specimens. A decrease in acetylcholinesterase activity, thought to be due to axonal degeneration, was found in all cases. An increase in S100 positivity was found in the majority of the diabetics and is due to Schwann cell proliferation which might have been a regeneration attempt after demyelination or axonal degeneration. **This combination is highly suggestive of a neurogenic etiology for diabetic cystopathy** [19].

Non-Neurogenic Hypotheses for Diabetic Cystopathy

There is significant clinical evidence supporting a neurologic etiology for diabetic cystopathy, but other factors likely contribute. These include **polyuria** from increased osmotic load [20,21], **oxidative stress** to nerve and muscle tissue [22,23], and **microvascular damage** [14]. **Mitochondria** as a source of reactive oxygen species have also been implicated in tissue damage due to hyperglycemia [24]. **Obesity** has been associated with urinary incontinence in multiple studies apart from diabetes [25–27], and is well correlated with type 2 diabetes but not type 1 diabetes. It likely plays a role in the LUTS seen in DM2. **Urothelial dysfunction** has also been suggested as a contributing factor in diabetic cystopathy [28].

Not every diabetic patient with LUTS, however, exhibits the classic findings of diabetic cystopathy. Some exhibit detrusor overactivity. For instance, Kaplan, Blaivas, and colleagues reviewed 182 consecutive urodynamic studies on diabetic patients and found that, contrary to the popular dogma, most of the patients affected by diabetes had detrusor hyperreflexia (100/182 or 55%) while only 42 (24%) exhibited impaired detrusor contractility, and 19 (10%) exhibited detrusor areflexia [18]. It is important to note that all of the subjects studied presented with a voiding complaint, and so this does not represent a balanced cross-section of the diabetic population, but rather a sampling of those already manifesting LUTS, which biases results.

With regard to LUTS, in the same investigation Kaplan and colleagues noted nocturia greater than twice per night was the most common symptom reported by diabetic subjects (87%). Urinary frequency (voiding at least every 2 hours) occurred in 74%. Urinary retention was noted in 17 patients, with 7 being secondary to bladder outlet obstruction in men exclusively, 9 secondary to detrusor areflexia (men and women), and “indeterminate” in 1. With regard to the type of diabetes, 37% were diet-controlled, 35% controlled with oral hypoglycemic agents, and 28% requiring insulin. Peripheral neuropathy was documented in 26% [18].

On the contrary, Yamaguchi and colleagues noted 4% of subjects in a large urodynamic database carried a diagnosis of diabetic neuropathy. These subjects were initially identified by neurologic exam (84/2300), with 71% reporting poor flow, 59% reporting hesitancy, 38% reporting sensation of residual urine. On urodynamic study, 48% demonstrated “underactive detrusor” (defined using the Schafer nomogram), 32% demonstrated impaired sensation (first sensation >300cc), and 57% reported retention (PVR >30cc). With regard to irritative voiding, as described by Kaplan and colleagues, 42% reported having urodynamic proven detrusor overactivity and 48% reported urinary urgency [29]. Although the Kaplan and Yamaguchi investigations both involve diabetics, it is likely the groups have too many confounding variables to draw conclusions about the role of diabetes alone in the reported symptoms and urodynamic findings. This is a common problem in the retrospective investigations exploring diabetic cystopathy. All diabetic subjects in the Yamaguchi group were selected because they had clinical manifestations neuropathy, a known risk factor for severe diabetic cystopathy [29]. In addition, 21/84 (25%) patients had suffered cerebral infarction in the Yamaguchi series, which is also likely to affect voiding function. In the this study, DM2 comprised 82% of subjects, while 18% had DM1, compared to the more mildly diabetic Kaplan subjects, where 37% were diet-controlled, 35% were DM2, and 28% were DM1. The type of diabetes may make a difference but the effects are unclear.

As mentioned previously there have been conflicting reports surrounding the difference between DM1 and DM2 with regard to effect on voiding function. Most of this work has focused on urinary incontinence. Lewis and colleagues performed a sample of households in the United States involving 10,678 women as part of the Health and Retirement Study. Urinary incontinence was reported by 22% of the respondents, and of these DM1 carried a significant increased odds of urinary incontinence (OR 1.6, 95% CI 1.28–2.09) while DM2 did not (OR 1.2, 95% CI 1.00–1.45). Questions were asked by a trained interviewer, and those related to incontinence sought to quantify the severity by replying how many days in

the last month they were incontinent. “0” was regarded as no incontinence, “1–15 days” as mild incontinence, and “16–30 days” was severe. DM1 was assessed by the self-reported need for insulin and DM2 by the need for oral medications alone. The patients ranged in age from 50–90 years. Limitations in performing activities of daily living, BMI, and age were also correlated with increased odds of incontinence [30]. It may be wrong to suggest that DM2 has no effect on urinary incontinence, however. Evidence taken from 81,000 women enrolled in the Nurse’s Health Study, a prospective observational study, noted a 1.28 relative risk of developing incontinence with DM2 compared to non-diabetic women. Diabetes and incontinence were determined by self-report [8].

Evidence from the Diabetes Prevention Program suggests that intensive lifestyle intervention, leading to weight loss, decreased the prevalence of urinary incontinence over a 3 year period compared to metformin alone or placebo alone [31]. This suggests intervention can be effective and provides motivation for early diagnosis.

LUTS May be Much More Common in Diabetics than Previously Thought

Changxiao and colleagues performed the first prospective population-based study on the prevalence of diabetic cystopathy that included urodynamic studies. They noted a 93% incidence of LUTS with 88% having positive findings on urodynamic studies [3]. 918 / 1,640 consecutive diabetic women exhibited impaired detrusor contraction, with a mean post void residual of 323cc. 131 patients were found to have detrusor areflexia by the authors’ urodynamic criteria, and of these 131 patients, 38 were noted to have impaired renal function and bilateral hydronephrosis, underscoring the potential for life threatening complications from diabetic cystopathy [3●●].

In summary, the clinical picture of diabetic cystopathy is variable based on the available published literature. The symptoms differ between DM1 and DM2, length of diagnosis, presence of neuropathy, age of the patient, and level of glucose control. Few of the clinical reports stratify patients based on all of these parameters, and it is likely that variability would decrease if this was done. The clinical literature is very helpful, however, in generating hypotheses for why diabetic cystopathy occurs.

Evidence from Animal Models

There is a noticeable lack of prospective clinical data on diabetic cystopathy, especially considering the magnitude of the problem and number of manuscripts published on diabetes overall. Much more has been published using animal models. These can be helpful to test hypotheses generated during clinical observation. Many investigators have described small animal bladder models for both DM1 and DM2, but large animal models are sparse.

Animal models for diabetic bladder dysfunction include mice, rats, rabbits, pigs, and dogs. Animal models are important in the study of diabetes and more broadly, metabolic syndrome, as it affects the urinary tract, because contributing factors can be isolated more easily in animals, genes can be manipulated, and tissue can be harvested easily to assess nerve density, protein glycosylation, tissue damage, as well as many other factors. Some

animal models, such as the mouse, have a compressed lifespan and lower cost, allowing more efficient study of disease processes that may take decades to develop in humans [20].

Ways to Induce Diabetes

Small Animal Models include animals treated with streptozocin or alloxan damage beta islet cells in the pancreas to reduce insulin production and produce durable hyperglycemia that mimics DM1. Some genetic small animal models include the Non Obese Diabetic mouse, the Akita mouse, and the diabetes prone Bio-Breeding rat. All of these develop DM1 spontaneously. Numerous genetic mouse models for DM2 exist, some involving multiple genes, thought to more accurately reflect the pathogenesis in humans. To differentiate the effects of diabetes from those of obesity on the urinary tract, non-diabetic genetic mouse models also exist [20].

Neuropathy

One animal model for DM1 has demonstrated an interesting difference in bladder function between streptozocin induced diabetic rats compared with diuretic – induced rats (achieved with 5% sucrose solution). Investigators noted an increased response to electrical field stimulation and increased bladder weight in both groups at 9 weeks when compared to age-matched controls [21]. The diuretic rats had a diminished purinergic bladder contraction response to electrical stimulation compared to controls, while the diabetic response remained elevated compared to controls. They concluded that hypertrophy alone was not responsible for the increased response to electrical stimulation, and that response to neurologic stimulus was different in the diabetic rat but not in the diuretic-induced rat [21].

Streptozocin induced DM1 in rats has demonstrated decreased nerve growth factor levels in bladder and dorsal root ganglia at levels L6 to S1. This was assayed at 12 weeks, suggesting a time dependent decrease in nerve growth factors [32].

Nerve Growth Factor as a Therapy

Decreased levels of nerve growth factor in diabetic animal models led to a 1997 phase 3 trial of recombinant human nerve growth factor involving 1019 patients with a diagnosis of polyneuropathy attributed to DM1 or DM2 [33]. The diagnosis of neuropathy was accomplished by a neurologist clinically. Validated questionnaires and nerve conduction studies were used as endpoints. The primary endpoint (Neuropathy Impairment Score for the Lower Limbs) and most secondary endpoints did not reach statistical significance. Some secondary endpoints did achieve significance in the treatment group. These were Global Symptom Assessment ($p=0.03$) and only 2 of the 32 items listed on the patient benefit questionnaire. These were “pain the feet” ($p=0.05$) and “6 month symptoms in the feet and legs” ($p=0.003$). The recombinant human nerve growth factor was given via an intramuscular route three times weekly [33]. This had previously demonstrated efficacy in phase 2 trials involving diabetic neuropathy as well as a trial including HIV patients with neuropathic pain [34,35].

Changes over time

Animal models have given us the first glimpse into how diabetic cystopathy might change over time. It is known that prolonged hyperglycemia results in accumulation of oxidative stress products in many tissue types [24]. Oxidative stress has been demonstrated in animal models for diabetic cystopathy [22,23]. Early after the development of DM1, the Streptozocin-induced rat has been noted to develop bladder hypertrophy and increased contractility [21,36]. Later in life, as disease is allowed to progress, peak voiding pressure decreases, more consistent with the classic definition of diabetic cystopathy [37●]. Based on this model, the authors propose that diabetic cystopathy develops in two phases. The early phase, where bladder hypertrophy and increased peak voiding pressure are mediated by osmotic diuresis and compensatory hypertrophy, results in storage problems. The latter phase, where oxidative stress from hyperglycemia results in a hypo-contractile bladder, results in emptying problems [20,37●]. It is not clear if other animal models exhibit this temporal change. Longitudinal trials in diabetic humans have not been done and might be justified on the basis of these findings.

Large Animal Models – Weaker Contraction and Evidence for Oxidative Stress

The rabbit with alloxan-induced diabetes is the first large animal to demonstrate detrusor underactivity [23]. Investigators assessed bladder strip contractility 6 months after induction of DM1 and found that the diabetic rabbit exhibited a much weaker response to potassium chloride and bethanechol than age matched controls or diuretic-induced bladder hypertrophy controls (57% and 40% decreased, respectively) [23]. Oxidative stress was compared in the animal model using lipid peroxidation, measured using malondialdehyde as a biomarker, as well as RT-PCR to measure the expression of the mRNA of the enzyme aldose reductase, a key enzyme in promoting oxidative stress through the depletion of antioxidants. Investigators found that malondialdehyde and peroxidase biproducts were all increased in the alloxan-induced diabetic rabbits compared with the normal and the sucrose-fed rabbits [23]. On the contrary, another large animal model for spontaneous DM2, the Ossabaw metabolic pig, has demonstrated decreased bladder muscle compliance and increased contractility [38,39]. Both of these large animal models might exhibit time-dependent change, as was noted in the streptozosin-induced rat, but these investigations remain to be done. This would add further justification for a prospective longitudinal study in diabetic humans.

Conclusion

The etiology of diabetic cystopathy likely has a significant neurologic component. Based on available animal evidence it is multifactorial with complex inter-relationships. Factors include neuropathy, polyuria, detrusor myopathy, urothelial-nerve-muscle interactions, oxidative stress, and microvascular compromise. These factors change over time, and in the human this time course is not known. It may be possible one day to determine the stage of diabetic neuropathy using urodynamic studies, LUTS, and possibly peripheral nerve testing. It may be possible to determine a predictable phenotype in patients with DM1 and DM2 based on the time since diagnosis and indicators of glucose control, such as Hgb A1c. The first step toward this goal will be to standardize the definition for diabetic cystopathy, and it

may be helpful to deliberately exclude urinary incontinence from that definition, as this may develop independent of diabetes.

Key to Abbreviations:

DM1	Type 1 Diabetes Mellitus
DM2	Type 2 Diabetes Mellitus
LUTS	Lower Urinary Tract Symptoms
AUA	American Urological Association
PVR	Post Void Residual
IPSS	International Prostate Symptom Score
HgbA1C	hemoglobin A1c
RT-PCR	reverse transcription polymerase chain reaction

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