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Diabetic Bladder Dysfunction

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Abstract

Objective—To review studies on diabetic bladder dysfunction (DBD), a common and bothersome complication of diabetes mellitus.

Data sources—We performed a search of the English literature through PubMed. The key words used were "diabetes" and "bladder dysfunction" or "cystopathy". Our own data and perspective are included in the discussion.

Study selection—Studies containing data relevant to DBD were selected. Because of the limited length of this article, we also referenced reviews that contain comprehensive amalgamations of relevant literature.

Results—The classic symptoms of DBD are decreased bladder sensation, increased bladder capacity, and impaired bladder emptying with resultant elevated post-void residual urine. However, recent clinical and experimental evidence indicate a strong presence of storage problems such as urge incontinence in diabetes. Recent studies of DBD in animal models of type 1 diabetes have revealed temporal effects of diabetes, causing an early phase of compensatory bladder function and a later phase of decompensated bladder function. The pathophysiology of DBD is multifactorial, including disturbances of the detrusor, urothelium, autonomic nerves, and urethra . Polyuria and hyperglycemia play important but distinctive roles in induction of bladder dysfunction in type 1 diabetes. Polyuria causes significant bladder hypertrophy in the early stage of diabetes, whereas oxidative stress in the bladder caused by chronic hyperglycemia may play an important role in the late stage failure of bladder function.

Conclusions—DBD includes time-dependent and mixed manifestations. The pathological alterations include muscle, nerve, and urothelium. Polyuria and hyperglycemia independently contribute to the pathogenesis of DBD. Treatments for DBD are limited. Future clinical studies on DBD in type 1 and type 2 DM should be investigated separately. Animal studies of DBD in type 2 diabetes are needed, from the natural history to mechanisms. Further understanding of the molecular mechanisms of DBD will provide multiple potential targets for therapeutic intervention.

Keywords

Diabetes; Bladder Dysfunction; Cystopathy; Complications

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INTRODUCTION

The U.S. Centers for Disease Control and Prevention estimated in 2010 that diabetes affects 25.8 million people in the U.S., 8.3% of the population, including 7.0 million diabetic individuals who were undiagnosed.[1] Among U.S. residents aged 65 years and older, the percentage with diabetes was estimated to be 26.9% (10.9 million people). Type 1 diabetes accounts for 5–10% of all diagnosed cases, whereas type 2 diabetes accounts for 90–95% of cases.[1] The total medical and indirect (work loss, disability, etc.) costs of diabetes and its complications were estimated to be $174 billion in the U.S. in 2007.[1] Continuation of this trend is expected due to the continuing rise in obesity, a major risk factor for type 2 diabetes. Diabetics live decades with the disease and are susceptible to numerous burdensome and costly complications. Urologic complications, including diabetic bladder dysfunction (DBD), sexual dysfunction, and urinary tract infections, are plausibly the most common, collectively affecting well over 50% of diabetic individuals.[2] Among those, the most common urologic complication of diabetes is DBD[3;4] or diabetic cystopathy.[5–9]

The term diabetic cystopathy was first used by Frimodt-Moller in 1976[5–7;10] to describe increased bladder capacity and post voiding residual volumes in diabetic patients, accompanied by decreased bladder sensation and contraction, which are generally symptoms of later stage bladder dysfunction in DM attributed to diabetic neuropathy.[11–13;8;14;15] DBD currently refers to an umbrella description for a group of clinical symptoms that encompass storage problems such as overactive bladder (OAB) and urge incontinence, voiding problems such as poor emptying or overflow incontinence, and other less clinically defined phenotypes such as decreased sensation and increased capacity.[3–9;16–18] The diverse symptoms of DBD include bladder overactivity, impaired bladder contractility, and areflexic bladder. Its prevalence among diabetic individuals has been estimated as being between 43 and 87%.[19;20] Although DBD is not life threatening, it affects quality of life substantially.

CLINICAL INVESTIGATION OF BLADDER DYSFUNCTION IN DIABETES

Varied symptoms of DBD in diabetic patients

The most common urodynamic findings in diabetic patients are impairment of bladder sensation, increased post-void residual urine volume, and decreased detrusor contractility. In a case of DBD in a non-obese adolescent girl with type 1 diabetes for 10 years, ultrasonography of the urinary tract showed a distended bladder with normal kidneys, and a urodynamic study indicated impaired bladder sensation, increased cystometric capacity, and detrusor areflexia.[21] However, inconsistencies with those “classic” findings have been found in recent clinical studies. Ueda et al. studied asymptomatic diabetic patients and found increased bladder volume at first sensation to void and a decrease in detrusor contractility, with resultant increased post void residual volume, but they also found a 25% incidence of detrusor overactivity.[22] A review by Kaplan and coworkers of urodynamic findings in 182 diabetic patients revealed 55% with detrusor overactivity and only 23% with impaired contractility, with 10% of patients areflexic and 11% “indeterminate”.[23] The mixed clinical picture of DBD has also been revealed in recent large-scale studies of urinary incontinence, in which diabetes was associated with a 30–70% increased risk of overall incontinence[24–26]

and a 50% increased risk of urge incontinence in women.[27;28] Thus, it is now clear that DBD manifestations are a combination of storage and voiding bladder problems.

The varied symptoms of DBD may be related to gender, age, concurrent bladder outlet obstruction, and duration of diabetes.[29] In a recent clinical study, several independent associations were found: female gender was associated with increased bladder capacity, male gender with both decreased bladder compliance and bladder outlet obstruction, old age with both low flow rate and outlet obstruction, detrusor instability with shorter duration of diabetes, and peripheral somatic neuropathy with low flow rate.[29] Recent evidence suggests that lower urinary tract (LUT) symptoms may occur more frequently among men with diabetes, with an increased risk estimated at 25% to nearly twofold in different studies.[30–32] In a study of type 2 diabetic men and women, age, duration of diabetes, poor metabolic control, post-void residual volume ≥100 ml, parasympathetic autonomic neuropathies (cardiac, esophageal, and gastric), retinopathy, and microalbuminuria all correlated with urodynamic findings of DBD.[17]

DBD is related to diabetes-induced peripheral polyneuropathy

Lee et al investigated the urodynamic characteristics and bladder sensory function in 86 consecutive women with type 2 diabetes who had not sought treatment for DBD.[16] From the urodynamic studies 34.9% of those women were classified with detrusor underactivity, 14.0% with detrusor overactivity, 12.8% with bladder outlet obstruction, and 38.4% with normal detrusor function. The detrusor underactivity group had impaired bladder emptying in cystometry and decreased sensation in intravesical current perception threshold testing. The detrusor overactivity group exhibited impaired storage and emptying function, but had similar current perception threshold values as the women with normal detrusor function. Those data indicate an association between poor emptying function and impaired bladder afferent pathways in diabetic women with detrusor underactivity. Peripheral neuropathy may also be involved in diabetes-related detrusor overactivity with impaired contractility. Ho et al reviewed urodynamic findings from 94 female type 2 diabetic patients, among whom 34 had been diagnosed as having overactive bladder (OAB).[33] Patients in the OAB group had significantly higher storage symptom scores and marginally higher voiding symptom scores than the patients without OAB, and on cystometry, significantly higher percentages of increased bladder sensation and detrusor overactivity were found in the OAB group. That study showed that the most frequent urodynamic finding in female diabetic patients with symptoms of OAB is increased bladder sensation, followed by detrusor overactivity.[33] In a study of men with diabetes and LUT symptoms who underwent urodynamic studies and neurological testing, both sensory deficits (high volume at first sensation) and motor deficits (detrusor underactivity and high post-void residual volume correlated significantly with both sensory and motor nerve conduction deficits, and high bladder capacity correlated with abnormal sympathetic skin responses as well.[34] An association of DBD with impaired sympathetic skin responses in diabetic patients was also reported in an earlier study.[35]

Limitations of clinical studies

First, the clinical studies discussed above have presented broadly varied estimates of the prevalence of LUT symptoms or bladder dysfunction in diabetic patients, reflecting the lack

of a validated set of clinically significant measures for diagnosing DBD.[36] Second, most previous studies on DBD did not differentiate between type 1 and type 2 diabetes, or adjust for other established risk factors such as aging and parity. Third, concurrent pathological conditions such as benign prostatic hyperplasia in men, neurological disorders, obesity, hypertension, and metabolic syndrome make it difficult to distinguish how diabetes per se contributes to the incidence or severity of DBD.

ANIMAL STUDIES OF BLADDER DYSFUNCTION IN DIABETES

Temporal changes of bladder function in type 1 diabetes rodent models

The demonstration of both storage and voiding problems among the clinical manifestations of DBD raised the question of whether those represent potentially concurrent pathologies, or if DBD follows a natural progression from storage problems to voiding problems. We demonstrated that the bladder in small rodent models of type 1 diabetes undergoes a temporal progression from an initial compensatory hypertrophic phase to a later decompensated or atonic phase.[37;38] Bladder function was observed in male C57BL/6 mice up to 20 weeks after induction of diabetes by streptozotocin (STZ), which destroys the pancreatic β-cells. Conscious cystometrograms showed increased peak voiding pressure (PVP) initially in both diabetic and diuretic mice compared with controls. However, in diabetic mice, PVP dropped by 12 weeks, and the emptying ability of the bladder had declined further at 20 weeks. Long-term insulin replacement effectively reversed most of the changes in bladder function.[38] We observed a similar temporal change from a compensatory to a decompensated bladder in STZ-diabetic Sprague Dawley rats.[37]

Multifactorial temporal changes in the bladder in diabetes

The traditional view recognized autonomic neuropathy as the sole pathophysiological cause of DBD.[5–9] That view considered decreased sensation of the bladder, with patients being unaware of bladder filling and lacking a desire to empty, to be the primary event resulting in high post-void residual volume and overflow incontinence, and presumed that it resulted from autonomic neuropathy. However, details of how loss of sensation could lead to the mixed clinical manifestations of DBD are unknown. That view has evolved to the belief currently held by most contemporary investigators that the pathophysiology of DBD is multifactorial, including disturbances of the bladder detrusor, autonomic nerves, and perhaps the urothelium,[4;14;18;39] as we and others have observed in diabetic animals.[4;37–52]

Myogenic changes in diabetes—*In vitro* experimental studies on detrusor smooth muscle (DSM) from animal models of diabetes have provided evidence for functional myogenic changes. Early studies showed decreased,[53] unchanged,[54] or increased [53;55] contractility of DSM strips from diabetic rats compared with controls. Our time course study showed that the contractility changes are time-dependent. Elevated contractile responses of DSM strips from STZ-diabetic rats to carbachol chloride, potassium chloride (KCl), adenosine 5'- triphosphate (ATP), and electric field stimulation peaked at 6–9 weeks, but at 12–20 weeks generally reverted towards those of controls.[37] Another group showed decreases in KCl- and carbachol-stimulated contractility of DSM strips from alloxan-induced diabetic rabbits in association with both the duration and level of hyperglycemia.[56]

An increase in muscarinic receptor density was found at both 2 and 8 weeks of STZ-induced diabetes.[57;58] An increase in β_1-receptor-mediated relaxation responses was found in isolated DSM strips from 8- to 10-week STZ- diabetic rats.[59] Another group found that pre-incubation of DSM strips with an α-1a- or α-1d-adrenergic receptor antagonist before electrical field stimulation decreased the contractile responses of strips from 8-week STZ-diabetic rats compared with DSM strips from control rats, although the mRNA levels of α-1a- and α-1d-adrenergic receptors were lower in the diabetic rats.[60] Those results suggested the possibility of alterations in presynaptic and autonomic receptor sensitivity.[60] The increased contractility of STZ-diabetic rat DSM may relate to increased neurotransmitter release, increased calcium channel activity, or enhanced calcium sensitivity.[55] Other studies showed that the activities of ion pumps such as the Na^+/K^+-ATPase and Ca^{2+}-ATPase pumps, important modulators of bladder smooth muscle tone, are impaired in STZ-diabetic rats.[61]

Morphologically, STZ-induced diabetes causes significant DSM hypertrophy in rats, as early as 1–2 weeks after STZ injection.[41] We showed that diuresis, which accompanies development of type 1 diabetes, independently induced DSM hypertrophy to the same extent as STZ when induced by addition of 5% sucrose to the drinking water.[41;43] The levels of the catalytic and regulatory subunits of calcineurin in DSM were increased in both diabetic and diuretic rats compared with controls, whereas the levels of total and phosphorylated Akt were unchanged, suggesting involvement of calcineurin in the development of the bladder hypertrophy.[43]

Urothelial changes in diabetes—The bladder urothelium is important for the regulation of permeability, transport, and endocytosis across the bladder wall. It has become increasingly clear that the urothelium is not only a passive barrier against urea and ion diffusion, but it can also function as a sensor controlling bladder function.[2;62] Studies from us and others showed increased urothelium mass in STZ-induced diabetic rats, with accompanying changes in both urothelial cell receptor expression and release of signaling molecules such as neurotransmitters.[41;46;63] Those changes may contribute to DBD by altering the normal two-way communication between urothelial cells and the underlying DSM cells and nerve endings.[4] In a recent study of urothelial morphology and gene expression in female rats 3, 9, and 20 weeks following STZ induction of diabetes compared with age-matched controls, electron microscopy revealed desquamation of superficial (umbrella) cells at 9 weeks of diabetes, indicating a possible breach in barrier function, followed by superficial urothelium repopulation by 20 weeks of diabetes.[46] mRNAs for the polyol pathway enzyme aldose reductase, nerve growth factor, and sonic hedgehog were upregulated in diabetic urothelium at all three time points, while significant upregulation of receptors associated with urothelium mechanosensation (transient receptor potential vanilloid subfamily member 1) and urothelium autocrine/paracrine signaling (acetylcholine receptors M2 and M3, purinergic receptors P2X2 and P2X3) were found at 20 weeks of diabetes. Those results suggest that compromised barrier function and alterations in urothelium mechanosensitivity and cell signaling in DM could contribute to bladder instability, hyperactivity, and altered bladder sensation by modulating activity of afferent nerve endings abutting the urothelium.[46]

Neuronal changes in diabetes—The neuronal control of bladder function involves sophisticated and complex interactions among the autonomic and somatic afferent and efferent pathways. Many studies have shown an association or causal link between diabetes-induced peripheral neuropathy and bladder dysfunction.[64;65] Steers et al showed significant abnormalities in afferent pathways innervating the bladder in STZ-induced diabetic rats.[66] A study in Goto-Kakizaki rats indicated that type 2 diabetes induces bladder sensory dysfunction, manifesting as slower bladder afferent conduction velocity, larger bladder capacity and greater hypocontractility to acetylcholine.[64] Normal rats treated with capsaicin, a C-fiber afferent neurotoxin, exhibit a number of similarities to diabetic rats.[67] Since capsaicin is known to affect predominately small myelinated and unmyelinated afferents, it is temping to speculate that diabetes affects a similar afferent neuron population. On the other hand, it has also been suggested that DBD is initiated by neuropathy in the efferent limb of the micturition reflex.[65] We used immunofluorescence staining of the nerve-specific marker neurofilament 200in bladder cross sections of rats to show that STZ-induced diabetes caused a significant reduction in nerve density in the muscle at 9 and 20 weeks, and in the mucosa/submucosa at 20 weeks.[42] Growth and survival of peripheral neurons can be supported by neurotrophic factors from target tissues. In rats 12 weeks after induction of diabetes with STZ, significantly decreased levels of nerve growth factor were observed in the bladder and in L6 to S1 dorsal root ganglia, which contain bladder afferent neurons.[68] This study suggested that loss of neurotrophic support to peripheral nerves may be related to neurodegeneration in the bladder in DM.

Limitations of animal studies

Most animal studies on DBD have used the STZ-induced type 1 diabetes model, yet 90–95% of diabetic individuals have type 2 diabetes. There are several differences between type 1 and type 2 diabetes that may lead to different phenotypes of DBD in the two diseases: a) Insulin is depleted in type 1 diabetes, whereas type 2 diabetics have different combinations of insulin resistance and lower insulin levels, with depletion of insulin generally occurring only at the late stage. b) Untreated hyperglycemia is more severe in type 1 than in type 2 diabetes. c) A large proportion of type 2 diabetes patients (30–80%) have metabolic syndrome,[69–72] including obesity (particularly central adiposity), elevated triglyceride levels, low high-density lipoprotein cholesterol levels, and hypertension, some or all of which may affect bladder function independently. Thus, more studies of DBD in type 2 diabetes and other animal models are needed.

THE PATHOGENESIS OF DBD

Unlike other organs, the bladder faces not only hyperglycemia in diabetes, but also an increased volume of urine. We believe that both polyuria and hyperglycemia contribute to DBD.

Polyuria and DBD

The addition of 5% sucrose to animals' drinking water results in significant increases in fluid consumption and volume of urine output, without changes in body weight or serum glucose concentration.[41;73] In both rats and rabbits, sucrose-induced diuresis causes rapid

and substantial bladder hypertrophy and increased bladder contractility, capacity, and compliance, similar to the initial changes observed after induction of diabetes in rats.[73] Those similarities suggest that bladder hypertrophy in diabetic animals may reflect a physical adaptation to increased urine production and may be a significant factor in the early compensated bladder function in diabetes. We observed that both STZ-induced diabetes and 5% sucrose-induced diuresis in rats were characterized by rapid, marked remodeling of the bladder wall, including hypertrophy, lumen dilation, and reorganization of the relative structural relationships among the detrusor muscle, urothelium, and collagen.[41] In mice, we also have shown that, after the initial similarities in bladder hypertrophy and remodeling in STZ-induced diabetes and 5% sucrose-induced diuresis , a transition to a decreased micturition pressure and increased residual volume occurs at a later stage in diabetic mice.[38] In the diuretic mice, the micturition pressure did not change, but the residual volume increased. Therefore, polyuria itself can induce altered bladder structure and function.[38]

Prolonged hyperglycemia, oxidative stress, and DBD

Hyperglycemia induces a number of metabolic changes within cells that cannot reduce glucose transport efficiently,[74] among which oxidative stress (OS) is prominent.[75] OS arises in cells with excessive glucose through increased oxidation of glucose in the tricarboxylic acid cycle, resulting in excessive production of electrons that are donated to molecular oxygen to generate the reactive oxygen species (ROS) superoxide.[74–76] Dr. Brownlee has proposed a unifying mechanism that links increased superoxide and other ROS generated from it with activation of four damaging pathways in diabetes, namely increased production of advanced glycation end products, activation of protein kinase C signaling, and increased flux through the hexosamine and polyol pathways.[74] The excess ROS cause, in turn, DNA strand breaks, activation of poly (ADP-ribose) polymerase, and inhibition of glyceraldehyde-3 phosphate dehydrogenase, culminating in activation of the four damaging pathways, which result in detrimental changes in gene expression and further exacerbation of OS.[74]

In addition to numerous studies on the role of OS in the pathogenesis of diabetic complications in the eye, nervous system, kidney, and cardiovascular system,[75] several investigators have reported OS increases in bladder tissues in diabetes.[56;77–79] Recently, we performed urinary diversion surgery to divert urine from the ureter to the vagina in rats, in order to identify the pathogenic roles of hyperglycemia without polyuria in the bladder after induction of diabetes.[45] We found significantly increased levels of nitrotyrosine and manganese superoxide dismutase in the bladder in rats with UD and diabetes, but not in rats with UD alone or 5% sucrose-induced diuresis without UD, compared with untreated control rats. Another study showed that the decrease in contractility of the detrusor smooth muscle in alloxan-induced diabetic rabbits is associated with increased lipid peroxidation products and overexpression of aldose reductase, the main enzyme of the polyol pathway.[56] Oxidative damage to smooth muscle cells can induce apoptosis, which may contribute to diabetic cystopathy.[77;78] Increased OS may also interrupt neurotrophins necessary for neuron survival,[80] such as nerve growth factor, thereby accelerating neurodegeneration in the bladder.

Role of urethral dysfunction in DBD

Storage and release of urine requires coordination between the urinary bladder and the external urethral sphincter. During urine storage, the bladder is quiescent and the sphincter is active, whereas during voiding, the bladder is active and the sphincter is inhibited.[81] The most notable change in urethral function with DM is increased outlet resistance .[82–85] Diabetes can cause external urethral sphincter dysfunction, impaired urethral smooth muscle relaxation and nitric oxide responsiveness, and increased urethral smooth muscle responsiveness to alpha(1)-adrenergic agonists.[85] Detrusor-sphincter dyssynergia was found in approximately 30% of diabetic rats, but never in controls.[85] Those changes can increase outlet resistance, leading to bladder remodeling and accommodation of larger post-void residual volume, thereby exacerbating the impact of impaired bladder contractility in DBD.[85]

TREATMENTS OF DBD

Little research has been published to guide practice in DBD management. Controlling the blood glucose level is the first step in the management of diabetes. However, controlling blood glucose does not necessarily prevent DBD, as the prevalence of DBD in patients on oral hypoglycemic treatment is 25%.[19] The treatment for DBD is basically conservative, aiming to eliminate symptoms.[18;86] If the major symptom is urine retention, treatment may involve a drug such as a cholinergic agent to promote better bladder emptying, scheduling voiding at regular intervals, and/or massaging the lower abdomen to help fully empty the bladder. Catheterization to drain the urine is sometimes required. If the most bothersome symptom is urine leakage, current treatments include medications such as anticholinergics, scheduled voiding, Kegel exercises to strengthen pelvic floor muscles, and surgical procedures such as pelvic sling or bladder neck suspension.[18]

No new therapies for either prevention or treatment of DBD have been approved, and only a few animal studies have been performed. Antioxidants can decrease the level of OS in the bladder and improve the bladder function in diabetic rats.[79;87] Cell-based therapies for DBD have shown promising results.[88;89] Transplantation of ex vivo-cultured healthy smooth muscle cells into the bladders of diabetic rats resulted in increased bladder contractile responses and decreased residual urine.[88] Stem cells have also been proposed to treat DBD due to their ability to reduce inflammation, prevent fibrosis, promote angiogenesis, recruit endogenous progenitor cells, and differentiate to replace damaged cells.[89] Adipose tissue-derived stem cells ameliorated DBD in rats fed a high-fat diet and treated with low-dose STZ to induce type 2 diabetes.[90] Although some stem cells differentiated into smooth muscle cells, a paracrine pathway was proposed to play the main role in this process.

CONCLUSIONS

Diabetes affects the nature and function of the bladder in a temporal fashion. The pathological alterations include muscle, nerve, and urothelium. Polyuria and hyperglycemia independently contribute to the pathogenesis of DBD in type 1 diabetes; comprehensive studies of the natural history and mechanisms of DBD in type 2 diabetes are needed. Future clinical studies on DBD in type 1 and type 2 DM should be investigated separately. The

available treatments for DBD are limited and inadequate. Further understanding of the molecular mechanisms of DBD will provide multiple potential targets for therapeutic intervention.

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REFERENCES

1. Centers for Disease Control and Prevention. National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services. Ref Type: Report; 2011.
2. Brown JS, Wessells H, Chancellor MB, Howards SS, Stamm WE, Stapleton AE, et al. Urologic complications of diabetes. Diabetes Care. 2005; 28:177–185. [PubMed: 15616253]
3. Baneerjee MK, Das AK, Basha A, Ganesan TS, Chandrasekhar S. Reversibility of diabetic bladder dysfunction with early and good control. J Assoc.Physicians India. 1985; 33:337–338. [PubMed: 4044498]
4. Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: current translational knowledge. J Urol. 2009; 182:S18–S26. [PubMed: 19846137]
5. Moller CF. Diabetic cystopathy.I: A clinical study of the frequency of bladder dysfunction in diabetics. Dan.Med.Bull. 1976; 23:267–278. [PubMed: 1009795]
6. Moller CF. Diabetic cystopathy.II: Relationship to some late-diabetic manifestations. Dan.Med.Bull. 1976; 23:279–287. [PubMed: 1009796]
7. Moller CF. Diabetic cystopathy.III:Urinary bladder dysfunction in relation to bacteriuria. Dan.Med.Bull. 1976; 23:287–291. [PubMed: 1009797]
8. Frimodt-Moller C. Diabetic cystopathy. A review of the urodynamic and clinical features of neurogenic bladder dysfunction in diabetes mellitus. Dan.Med.Bull. 1978; 25:49–60. [PubMed: 344005]
9. Kaplan SA, Blaivas JG. Diabetic cystopathy. J Diabet.Complications. 1988; 2:133–139. [PubMed: 2975663]
10. Moller CF, Olesen KP. Diabetic cystopathy. IV: Micturition cystourethrography compared with urodynamic investigation. Dan.Med.Bull. 1976; 23:291–294. [PubMed: 1009798]
11. Bladder Research Progress Review Group. Overcoming Bladder Disease: A Strategic Plan for Research. A report of the bladder research progress review group, National Institute of Diabetes and Digestive and Kidney Diseases, National Institues of Health. Chapter 10, 133; 2002. Urologic complications of diabetes mellitus. Ref Type: Report
12. Bladder Research Progress Review Group. Urologic complications of diabetes mellitus in overcoming bladder disease: a strategic plan for research. A report of the NIH-NIDDK bladder research progress review group. 2004 Ref Type: Report.
13. Daneshgari F, Moore C. Diabetic uropathy. Semin.Nephrol. 2006; 26:182–185. [PubMed: 16530610]
14. Gomez CS, Kanagarajah P, Gousse AE. Bladder dysfunction in patients with diabetes. Curr.Urol Rep. 2011; 12:419–426. [PubMed: 21894526]
15. Hill SR, Fayyad AM, Jones GR. Diabetes mellitus and female lower urinary tract symptoms: a review. Neurourol.Urodyn. 2008; 27:362–367. [PubMed: 18041770]
16. Lee WC, Wu HP, Tai TY, Yu HJ, Chiang PH. Investigation of urodynamic characteristics and bladder sensory function in the early stages of diabetic bladder dysfunction in women with type 2 diabetes. J Urol. 2009; 181:198–203. [PubMed: 19013605]

17. Kebapci N, Yenilmez A, Efe B, Entok E, Demirustu C. Bladder dysfunction in type 2 diabetic patients. Neurourol.Urodyn. 2007; 26:814–819. [PubMed: 17455274]
18. Golbidi S, Laher I. Bladder dysfunction in diabetes mellitus. Front Pharmacol. 2010; 1:136. [PubMed: 21833175]
19. Frimodt-Moller C. Diabetic cystopathy: epidemiology and related disorders. Ann.Intern.Med. 1980; 92:318–321. [PubMed: 7356221]
20. Lee WC, Wu HP, Tai TY, Liu SP, Chen J, Yu HJ. Effects of diabetes on female voiding behavior. J Urol. 2004; 172:989–992. [PubMed: 15311019]
21. Alves C, Sobral MM. Autonomic bladder dysfunction in an adolescent with type 1 diabetes. J Pediatr.Endocrinol.Metab. 2010; 23:401–402. [PubMed: 20583546]
22. Ueda T, Tamaki M, Kageyama S, Yoshimura N, Yoshida O. Urinary incontinence among community-dwelling people aged 40 years or older in Japan: prevalence, risk factors, knowledge and self-perception. Int.J.Urol. 2000; 7:95–103. [PubMed: 10750888]
23. Kaplan SA, Te AE, Blaivas JG. Urodynamic findings in patients with diabetic cystopathy. J.Urol. 1995; 153:342–344. [PubMed: 7815578]
24. Brown JS, Seeley DG, Fong J, Black DM, Ensrud KE, Grady D. Urinary incontinence in older women: who is at risk? Study of Osteoporotic Fractures Research Group. Obstet.Gynecol. 1996; 87:715–721. [PubMed: 8677073]
25. Wetle T, Scherr P, Branch LG, Resnick NM, Harris T, Evans D, et al. Difficulty with holding urine among older persons in a geographically defined community: prevalence and correlates. J.Am.Geriatr.Soc. 1995; 43:349–355. [PubMed: 7706622]
26. Diokno AC, Brock BM, Herzog AR, Bromberg J. Medical correlates of urinary incontinence in the elderly. Urology. 1990; 36:129–138. [PubMed: 2385880]
27. Brown JS, Grady D, Ouslander JG, Herzog AR, Varner RE, Posner SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet.Gynecol. 1999; 94:66–70. [PubMed: 10389720]
28. Brown JS, Nyberg LM, Kusek JW, Burgio KL, Diokno AC, Foldspang A, et al. Proceedings of the National Institute of Diabetes and Digestive and Kidney Diseases International Symposium on Epidemiologic Issues in Urinary Incontinence in Women. Am.J.Obstet.Gynecol. 2003; 188:S77–S88. [PubMed: 12825024]
29. Esteghamati A, Rashidi A, Nikfallah A, Yousefizadeh A. The association between urodynamic findings and microvascular complications in patients with long-term type 2 diabetes but without voiding symptoms. Diabetes Res.Clin.Pract. 2007; 78:42–50. [PubMed: 17368856]
30. Joseph MA, Harlow SD, Wei JT, Sarma AV, Dunn RL, Taylor JM, et al. Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. Am.J Epidemiol. 2003; 157:906–914. [PubMed: 12746243]
31. Klein BE, Klein R, Lee KE, Bruskewitz RC. Correlates of urinary symptom scores in men. Am.J Public Health. 1999; 89:1745–1748. [PubMed: 10553401]
32. Michel MC, Mehlburger L, Schumacher H, Bressel HU, Goepel M. Effect of diabetes on lower urinary tract symptoms in patients with benign prostatic hyperplasia. J Urol. 2000; 163:1725–1729. [PubMed: 10799169]
33. Ho CH, Tai HC, Yu HJ. Urodynamic findings in female diabetic patients with and without overactive bladder symptoms. Neurourol.Urodyn. 2010; 29:424–427. [PubMed: 19283863]
34. Bansal R, Agarwal MM, Modi M, Mandal AK, Singh SK. Urodynamic profile of diabetic patients with lower urinary tract symptoms: association of diabetic cystopathy with autonomic and peripheral neuropathy. Urology. 2011; 77:699–705. [PubMed: 21195463]
35. Ueda T, Yoshimura N, Yoshida O. Diabetic cystopathy: relationship to autonomic neuropathy detected by sympathetic skin response. J.Urol. 1997; 157:580–584. [PubMed: 8996363]
36. Brown JS. Diabetic cystopathy--what does it mean? J Urol. 2009; 181:13–14. [PubMed: 19012909]
37. Daneshgari F, Liu G, Imrey PB. Time dependent changes in diabetic cystopathy in rats include compensated and decompensated bladder function. J Urol. 2006; 176:380–386. [PubMed: 16753447]

38. Daneshgari F, Huang X, Liu G, Bena J, Saffore L, Powell CT. Temporal differences in bladder dysfunction caused by diabetes, diuresis, and treated diabetes in mice. Am.J Physiol Regul.Integr.Comp Physiol. 2006; 290:R1728–R1735. [PubMed: 16439670]
39. Yoshimura N, Chancellor MB, Andersson KE, Christ GJ. Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy. BJU.Int. 2005; 95:733–738. [PubMed: 15794773]
40. Liu G, Daneshgari F. Alterations in neurogenically mediated contractile responses of urinary bladder in rats with diabetes. Am.J.Physiol Renal Physiol. 2005; 288:F1220–F1226. [PubMed: 15687244]
41. Liu G, Daneshgari F. Temporal diabetes- and diuresis-induced remodeling of the urinary bladder in the rat. Am.J Physiol Regul.Integr.Comp Physiol. 2006; 291:R837–R843. [PubMed: 16513765]
42. Liu G, Li M, Vasanji A, Daneshgari F. Temporal diabetes and diuresis-induced alteration of nerves and vasculature of the urinary bladder in the rat. BJU.Int. 2011; 107:1988–1993. [PubMed: 21087392]
43. Liu G, Li M, Daneshgari F. Calcineurin and Akt expression in hypertrophied bladder in STZ-induced diabetic rat. Exp.Mol.Pathol. 2012; 92:210–216. [PubMed: 22305959]
44. Daneshgari F, Leiter EH, Liu G, Reeder J. Animal models of diabetic uropathy. J Urol. 2009; 182:S8–S13. [PubMed: 19846143]
45. Xiao N, Wang Z, Huang Y, Daneshgari F, Liu G. Roles of polyuria and hyperglycemia in bladder dysfunction in diabetes. J Urol. 2013; 189:1130–1136. [PubMed: 22999997]
46. Hanna-Mitchell AT, Ruiz GW, Daneshgari F, Liu G, Apodaca G, Birder LA. Impact of diabetes mellitus on bladder uroepithelial cells. Am.J Physiol Regul.Integr.Comp Physiol. 2013; 304:R84–R93. [PubMed: 23174855]
47. Tammela TL, Briscoe JA, Levin RM, Longhurst PA. Factors underlying the increased sensitivity to field stimulation of urinary bladder strips from streptozotocin-induced diabetic rats. Br.J.Pharmacol. 1994; 113:195–203. [PubMed: 7812610]
48. Tammela TL, Leggett RE, Levin RM, Longhurst PA. Temporal changes in micturition and bladder contractility after sucrose diuresis and streptozotocin-induced diabetes mellitus in rats. J.Urol. 1995; 153:2014–21. [PubMed: 7752386]
49. Poladia DP, Bauer JA. Early cell-specific changes in nitric oxide synthases, reactive nitrogen species formation, and ubiquitinylation during diabetes-related bladder remodeling. Diabetes Metab Res.Rev. 2003; 19:313–319. [PubMed: 12879409]
50. Poladia DP, Bauer JA. Oxidant driven signaling pathways during diabetes: role of Rac1 and modulation of protein kinase activity in mouse urinary bladder. Biochimie. 2004; 86:543–551. [PubMed: 15388231]
51. Poladia DP, Bauer JA. Functional, structural, and neuronal alterations in urinary bladder during diabetes: investigations of a mouse model. Pharmacology. 2005; 74:84–94. [PubMed: 15714007]
52. Poladia DP, Schanbacher B, Wallace LJ, Bauer JA. Innervation and connexin isoform expression during diabetes-related bladder dysfunction: early structural vs. neuronal remodelling. Acta Diabetol. 2005; 42:147–152. [PubMed: 16258738]
53. Longhurst PA, Belis JA. Abnormalities of rat bladder contractility in streptozotocin-induced diabetes mellitus. J.Pharmacol.Exp.Ther. 1986; 238:773–777. [PubMed: 3746663]
54. Luheshi GN, Zar MA. The effect of streptozotocin-induced diabetes on cholinergic motor transmission in the rat urinary bladder. Br.J.Pharmacol. 1991; 103:1657–1662. [PubMed: 1657263]
55. Waring JV, Wendt IR. Effects of streptozotocin-induced diabetes mellitus on intracellular calcium and contraction of longitudinal smooth muscle from rat urinary bladder. J.Urol. 2000; 163:323–330. [PubMed: 10604384]
56. Changolkar AK, Hypolite JA, DiSanto M, Oates PJ, Wein AJ, Chacko S. Diabetes induced decrease in detrusor smooth muscle force is associated with oxidative stress and overactivity of aldose reductase. J Urol. 2005; 173:309–313. [PubMed: 15592102]
57. Tong YC, Chin WT, Cheng JT. Alterations in urinary bladder M2-muscarinic receptor protein and mRNA in 2-week streptozotocin-induced diabetic rats. Neurosci.Lett. 1999; 277:173–176. [PubMed: 10626841]

58. Tong YC, Cheng JT. Alteration of M(3) subtype muscarinic receptors in the diabetic rat urinary bladder. Pharmacology. 2002; 64:148–151. [PubMed: 11834891]
59. Kubota Y, Nakahara T, Mitani A, Maruko T, Sakamoto K, Ishii K. Augmentation of rat urinary bladder relaxation mediated by beta1-adrenoceptors in experimental diabetes. Eur.J Pharmacol. 2003; 467:191–195. [PubMed: 12706474]
60. Gonulalan U, Kosan M, Hafez G, Arioglu E, Akdemir O, Ozturk B, et al. The effect of diabetes mellitus on alpha1-adrenergic receptor subtypes in the bladder of rats. Urology. 2012; 80:951–916. [PubMed: 22901825]
61. Mustafa S. Effect of diabetes on the ion pumps of the bladder. Urology. 2013; 81:211–221. [PubMed: 23153938]
62. Birder LA. Urothelial signaling. Handb.Exp.Pharmacol. 2011:207–231. [PubMed: 21290228]
63. Pitre DA, Ma T, Wallace LJ, Bauer JA. Time-dependent urinary bladder remodeling in the streptozotocin-induced diabetic rat model. Acta Diabetol. 2002; 39:23–27. [PubMed: 12043935]
64. Aizawa N, Homma Y, Igawa Y. Characteristics of lower urinary tract dysfunction and bladder afferent nerve properties in type 2 diabetic goto-kakizaki rats. J Urol. 2013; 189:1580–1587. [PubMed: 23103236]
65. Paro M, Prashar A, Prosdocimi M, Cherian PV, Fiori MG, Sima AA. Urinary bladder dysfunction in the BB/W diabetic rat: effect of ganglioside treatment on functional and structural alterations. J.Urol. 1994; 151:781–786. [PubMed: 8309006]
66. Steers WD, Mackway-Gerardi AM, Ciambotti J, de Groat WC. Alterations in neural pathways to the urinary bladder of the rat in response to streptozotocin-induced diabetes. J.Auton.Nerv.Syst. 1994; 47:83–94. [PubMed: 7514623]
67. Cheng CL, Ma CP, de Groat WC. Effects of capsaicin on micturition and associated reflexes in rats. Am.J.Physiol. 1993; 265:R132–R138. [PubMed: 8342677]
68. Sasaki K, Chancellor MB, Phelan MW, Yokoyama T, Fraser MO, Seki S, et al. Diabetic cystopathy correlates with a long-term decrease in nerve growth factor levels in the bladder and lumbosacral dorsal root Ganglia. J.Urol. 2002; 168:1259–1264. [PubMed: 12187278]
69. Cull CA, Jensen CC, Retnakaran R, Holman RR. Impact of the metabolic syndrome on macrovascular and microvascular outcomes in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study 78. Circulation. 2007; 116:2119–2126. [PubMed: 17967769]
70. Kumar SV, Nagesh A, Leena M, Shravani G, Chandrasekar V. Incidence of metabolic syndrome and its characteristics of patients attending a diabetic outpatient clinic in a tertiary care hospital. J Nat.Sci Biol Med. 2013; 4:57–62. [PubMed: 23633836]
71. Osuji CU, Nzerem BA, Dioka CE, Onwubuya EI. Metabolic syndrome in newly diagnosed type 2 diabetes mellitus using NCEP-ATP III, the Nnewi experience. Niger.J Clin.Pract. 2012; 15:475–480. [PubMed: 23238201]
72. Imam SK, Shahid SK, Hassan A, Alvi Z. Frequency of the metabolic syndrome in type 2 diabetic subjects attending the diabetes clinic of a tertiary care hospital. J Pak.Med.Assoc. 2007; 57:239–242. [PubMed: 17571479]
73. Longhurst PA, Wein AJ, Levin RM. In-vivo urinary bladder function in rats following prolonged diabetic and non-diabetic diuresis. Neurourol Urodyn. 1990; 9:171–178.
74. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005; 54:1615–1625. [PubMed: 15919781]
75. Rolo AP, Palmeira CM. Diabetes and mitochondrial function: Role of hyperglycemia and oxidative stress. Toxicol.Appl.Pharmacol. 2006; 212:167–178. [PubMed: 16490224]
76. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001; 414:813–820. [PubMed: 11742414]
77. Beshay E, Carrier S. Oxidative stress plays a role in diabetes-induced bladder dysfunction in a rat model. Urology. 2004; 64:1062–1067. [PubMed: 15533519]
78. Kanika ND, Chang J, Tong Y, Tiplitsky S, Lin J, Yohannes E, et al. Oxidative stress status accompanying diabetic bladder cystopathy results in the activation of protein degradation pathways. BJU.Int. 2011; 107:1676–1684. [PubMed: 21518418]
79. Ha US, Bae WJ, Kim SJ, Yoon BI, Jang H, Hong SH, et al. Protective effect of cyanidin-3-O-beta-D-glucopyranoside fraction from mulberry fruit pigment against oxidative damage in

streptozotocin-induced diabetic rat bladder. Neurourol.Urodyn. 2013; 32:493–499. [PubMed: 23129268]

80. Whitmire W, Al-Gayyar MM, Abdelsaid M, Yousufzai BK, El-Remessy AB. Alteration of growth factors and neuronal death in diabetic retinopathy: what we have learned so far. Mol.Vis. 2011; 17:300–308. [PubMed: 21293735]
81. Andersson KE, Wein AJ. Pharmacology of the lower urinary tract: basis for current and future treatments of urinary incontinence. Pharmacol.Rev. 2004; 56:581–631. [PubMed: 15602011]
82. Christ GJ, Bushman W, Fraser MO. Impact of diabetes and obesity on the prostate and urethra: implications to improved bladder dysfunction understanding and treatment. J Urol. 2009; 182:S38–S44. [PubMed: 19846131]
83. Liu G, Lin YH, Yamada Y, Daneshgari F. External urethral sphincter activity in diabetic rats. Neurourol.Urodyn. 2008; 27:429–434. [PubMed: 18351620]
84. Torimoto K, Fraser MO, Hirao Y, de Groat WC, Chancellor MB, Yoshimura N. Urethral dysfunction in diabetic rats. J Urol. 2004; 171:1959–1964. [PubMed: 15076321]
85. Yang Z, Dolber PC, Fraser MO. Diabetic urethropathy compounds the effects of diabetic cystopathy. J Urol. 2007; 178:2213–2219. [PubMed: 17870107]
86. Hunter KF, Moore KN. Diabetes-associated bladder dysfunction in the older adult (CE). Geriatr.Nurs. 2003; 24:138–145. [PubMed: 12813425]
87. Ustuner MC, Kabay S, Ozden H, Guven G, Yucel M, Olgun EG, et al. The protective effects of vitamin E on urinary bladder apoptosis and oxidative stress in streptozotocin-induced diabetic rats. Urology. 2010; 75:902–906. [PubMed: 19683803]
88. Gopinath C, Ponsaerts P, Fransen E, Boeykens N, Pauwels P, Wyndaele JJ. Smooth muscle cell transplantation improves bladder contractile function in streptozocin-induced diabetic rats. Cytotherapy. 2013; 15:869–878. [PubMed: 23731765]
89. Vaegler M, Lenis AT, Daum L, Amend B, Stenzl A, Damaser MS, et al. Stem cell therapy for voiding and erectile dysfunction. Nat.Rev.Urol. 2012
90. Zhang H, Qiu X, Shindel AW, Ning H, Ferretti L, Jin X, et al. Adipose tissue-derived stem cells ameliorate diabetic bladder dysfunction in a type II diabetic rat model. Stem Cells Dev. 2012; 21:1391–1400. [PubMed: 22008016]