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Lower Urinary Tract Symptoms in Women with Diabetes Mellitus: A Current Review

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Abstract A literature review of the most current publications studying lower urinary tract symptoms (LUTS) and findings in diabetic women was conducted including articles from January 2013 to April 2014. Current reports consistently note that aging and obesity are significantly associated with worsened LUTS in diabetic women. Glucosuria has variable effects on urodynamic parameters and LUTS, but has a significant association with urinary tract infection (UTI) and incontinence at clinically relevant numbers, such as HbA1C values. The presence of severe nocturia in diabetic patients warrants careful surveillance for cardiovascular risks given the significant association with mortality. Diabetics appear to be at higher risk for colonization with the virulent, extended-spectrum, β-lactamase-producing *Escherichia coli* and *Klebsiella* species in UTI. Novel therapies in glycemic control and for diabetic bladder dysfunction are undergoing animal model trials with encouraging results. The most promising of these includes stem cell therapy, although a need exists for human studies.

Keywords Diabetes mellitus and lower urinary tract symptoms · Stress urinary incontinence · Urge incontinence · Overactive bladder · Urinary frequency · Urgency · Nocturia

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Introduction

The increased risks of lower urinary tract symptoms (LUTS) in diabetic patients have been studied at length. A current literature review was conducted from the most recent publications on findings and recommendations on lower urinary tract symptomatology in diabetic women.

Methods

A literature review was conducted using Ovid and PubMed to include studies in English that were published from January 2013 until April 2014. Search terms included: lower urinary tract symptoms, stress urinary incontinence, nocturia, urinary urgency, urinary frequency, nocturia, cystitis, urinary tract infection, and neurogenic bladder. These terms were each meshed with the search terms: diabetic women and diabetes mellitus (DM). Randomized, controlled trials (RCT), cohort studies, case-control studies, and women-only case reports were included. Excluded papers included: publications prior to Jan 1, 2013, one paper addressing solely a specific subpopulation of women, a case series on Wolfram syndrome that encompassed components of diabetes and enuresis found to be outside of the scope of this report, and papers not published in English. Literature citations necessary for background epidemiology were exempt from the exclusion criteria.

Epidemiology

Several publications have indicated the strong associations between LUTS in women with DM. In a cohort study of over 1,800 women, the prevalence of urinary incontinence (UI) was found to be 33 % among diabetics, which is in accordance with previous reports in the literature [1–5]. Of the 155 non-

diabetic women who had a family history of DM, 66 (43 %) were already incontinent ($p<0.01$) [1]. In examination of the prevalence of stress, urge, and mixed urinary incontinence and associated risk factors in 2,763 postmenopausal women, Brown et al. reported a significantly higher prevalence in diabetic women compared to non-diabetic women [2], comparable to the results of other investigators [2, 3, 6]. Ebbesen et al. investigated the association between DM and UI, including the possible influence of DM on the severity of incontinence, in a cross-sectional, population-based study from Norway. The prevalence of UI among women with diabetes was 39 % compared to 26 % in women without DM, and those with DM had significantly more urge and mixed incontinence after adjusting for cofounders. The association between DM and severe incontinence was stronger than the association between DM and any incontinence [7]. In a study of UI risk factors in middle-aged women from the Nurses Health Study, after adjusting for BMI and many other potential confounding factors, type II DM was associated with a modest, but statistically higher increase in the odds of frequent incontinence (OR, 1.18; 95 % CI, 1.10–1.26) and severe incontinence (OR, 1.30; 95 % CI, 1.20–1.41) [8]. However, the mechanistic relationship of increased risk for urinary incontinence among diabetic women remains poorly understood.

Diabetics are particularly at risk for urinary tract infection (UTI), with a prevalence of 21–25.3 %, an adjusted odds ratio of 1.24–1.96, and a reported incidence of 91.5/1,000 person-years specifically in women [9–13]. The most common site of infection in diabetic patients is the urinary tract [11].

Known Effects of DM on Bladder Dysfunction

Overactive Bladder and Urgency

A component of bladder dysfunction secondary to diabetes lies in storage issues such as overactive bladder (OAB). In their cross-sectional study, Bani-Issa et al. found obesity and increased age to be significant correlates for urge incontinence in diabetics [14].

Palleschi et al. showed an increase in OAB symptoms among type II diabetics as compared to healthy controls via the Overactive Bladder Questionnaire (OAB-q), a specific investigative tool developed for OAB diagnosis. Further, significant correlations between increasing age and progression of DM were found with increasing OAB symptoms [15]. In a large, cross-sectional sample of Kurdish women assessing the prevalence of urinary incontinence subtypes (stress, urge, and mixed), DM was among the significant risk factors [16]. Urgency incontinence is also more commonly reported in diabetic women with PVR≥100 mL [17].

Chung et al. showed that the rate of OAB was 28.8 % among diabetic patients with nocturia and was significantly associated with nocturia (OR 2.26) after adjustment for age and duration of DM [18••].

Nocturia

When defining nocturia as rising ≥2 times per night to void, a rate of 59.6 % was found among type II DM patients answering a self-administered questionnaire. Severe nocturia (rising ≥3 times per night) was reported among 25.3 %, which also significantly increased with age and the presence of OAB symptoms. Other risk factors associated with nocturia and severe nocturia included: history of stroke, calcium channel blocker use, hypertension, waist circumference greater than standard, albuminuria, higher serum creatinine level, high-sensitivity C-reactive protein after adjustment for age, duration of DM, and the presence of OAB. Importantly, severe nocturia increased mortality (OR 1.93) independent of age and DM duration, and had a higher mortality rate compared to diabetics without severe nocturia (6.1 vs. 2.4 %, $P=0.001$) in 2.5 years of follow-up [18••].

Neurogenic Bladder

The increased risk of bladder storage issues, such as poor emptying and overflow, in diabetics has been shown throughout the historical litera4ture [17, 19].

A thorough review article commented on the pathophysiology and clinical manifestations of diabetic nephropathy as it pertains to the bladder. While often asymptomatic in the early stages of diabetes despite demonstrable bladder abnormality, impaired bladder sensation is usually the first manifestation of lower urinary tract involvement. Micturition reflexes can become delayed due to diminished bladder sensation with increases in bladder capacity and urinary retention that usually occur asymptomatically. Patients are frequently unaware of bladder dysfunction until they have a urinary tract infection secondary to increased residual urine volume. The common symptoms are straining, hesitation, and weakness of stream. Diabetic neurogenic bladder can be characterized by impaired sensation of bladder fullness, which leads to overstretched bladder, reduced bladder contractility, increased residual urine, and impaired uroflow [19]. Lee et al. utilized electrophysiology to reveal that hyposensitivity of unmyelinated C-fiber afferents at the distal extremities is an indicator of early-stage diabetic bladder dysfunction in type II diabetic women. The C-fiber dysfunction at the distal extremities seems concurrent with vesical C-fiber neuropathy, and may be a sentinel explanation for the development of early diabetic bladder dysfunction among female patients [20]. The neurogenic dysfunction of the diabetic bladder typically evolves in a time-dependent progression of both storage and voiding problems. The early phase manifests as detrusor overactivity, leading to urinary frequency and urgency. However, over time,

progressive oxidative stress and neuropathy lead to decompensation of the detrusor musculature, thereby leading to an atonic bladder [21, 22••]. In their recent review article, Liu and Daneshgari note the need for more diabetic animal model studies that specifically investigate type II DM. They reference the prior studies of Daneshgari et al. that showed the bladder in rodent models of type I diabetes undergoes a temporal progression from an initial compensatory hypertrophic phase to a later decompensated or atonic phase. Conscious cystometrograms showed increased peak voiding pressure (PVP) initially in both diabetic and diuretic mice compared with controls. However, in diabetic mice, PVP dropped after 12 weeks, and the emptying ability of the bladder declined further at 20 weeks. Long-term insulin replacement effectively reversed most of the changes in bladder function [23, 24].

A post-void residual (PVR) of ≥100 was found among 12 % of diabetic women, and these patients were more likely to report obstructive voiding symptoms than women with PVR<50 mL. Poorer glycemic control was associated with an increased likelihood of PVR≥100 mL (OR 1.30, CI 1.06–1.59 per 1.0-U increase in HbA1c) [17]. Associations between glycemic control and urinary incontinence have shown inconsistent results. In a questionnaire study of over 6,000 diabetic women, HbA1c levels were not associated with the presence or absence of urinary incontinence. However, among women reporting incontinence, an HbA1c level≥9 % was associated with more limitations due to incontinence than an HbA1c level<6 % [25].

In a streptozotocin-induced-diabetes rat model of neurogenic bladder dysfunction, the activation of bombesin receptors triggered contractions and thus facilitated frequency of voiding in >80 % of rats when the bladder was filled to a subthreshold voiding volume. The authors suggest that bombesin receptors may be targeted for therapy in conditions associated with poor detrusor contraction such as an underactive bladder condition [26]. A similar diabetic rat model found that berberine increases the neurogenic contractile response mainly via the presynaptic acetylcholine release, taking advantage of a major alkaloid component of *Coptidis Rhizoma*, a principal therapy used in China to treat DM [27].

Urodynamic Findings

Urodynamic study (UDS) results for diabetic women appear consistent with the symptom profile and also parallel the findings in non-diabetic women with LUTS [19, 22••, 28, 29]. Diabetic neuropathy can be manifested on urodynamics by findings of reduced bladder contractility, increased residual urine, and impaired uroflow [19]. The early phase of the diabetic bladder manifests as detrusor overactivity [21, 22••]. Previously, Kaplan et al. have shown that classical descriptions of diabetic cystopathy including decreased bladder sensation, increased bladder capacity, and impaired detrusor contractility were not the most common urodynamic diagnoses. Instead, the UDS findings were variable, including detrusor hyperreflexia, impaired detrusor contractility, detrusor areflexia, and bladder outlet obstruction [30]. Additionally, when cystometric studies were conducted on 23 elderly diabetic patients, a variety of UDS results were shown, including: normal voluntary contractions of the bladder, voluntary contractions of a low magnitude, urinary incontinence associated with involuntary bladder contractions, and even a lack of involuntary contractions further supporting that late-stage diabetics do not uniformly present with acontractile bladders [31].

In a prospective study of 1,640 diabetic women in China, 88 % had positive urodynamic findings [28]. A study investigating factors associated with fecal incontinence in women with LUTS (who showed detrusor pressure at maximum flow on UDS) showed diabetes to be a significant factor by multivariate analysis [32]. The presence of diabetes was significantly associated with women who had detrusor overactivity and impaired contractility compared to women with detrusor overactivity whose contractility was preserved [33].

In a rat model of diabetic cystopathy, transcutaneous electrical nerve stimulation (TENS) treatment for three weeks ameliorated contractile responses compared to controls. Furthermore, TENS significantly increased bladder wet weight, volume threshold for micturition and reduced PVR, and cAMP content of the bladder [29].

The Role of DM in UTI

Infectious Cystitis

Pathophysiology

UTI is a common complication of diabetic patients [10, 34•, 35–37, 38•]. One proposed mechanism is the potential causative factor of glucosuria [39]. Often the clinical question arises of whether optimizing glycemic control would alleviate LUTS. Investigators have found an increased risk of UTI and higher PVR with poor glycemic control [17, 34•].

A literature review of women aged 65 years and older cited DM as a key risk factor for UTI [35]. A descriptive, cross-sectional study among diabetic men and women found that 21 % of the total patients had culture-positive UTIs, reaching statistical significance among women versus men. Asymptomatic bacteriuria was also more common in females. UTI was common among those with prolonged duration of diabetes and among those receiving insulin as compared to oral medications [10].

A non-randomized, prospective, observational study found the frequency of UTI among pyuric DM patients to be 59/97 (60.82 %). The prevalence of culture-negative, sterile pyuria was found to be 38/97 (39.17 %). Urinary tract infection was found more frequently in females with associated lower urinary tract symptoms and flank pains. Stone disease, obstructed pelvicalyceal system, proteinuria, high serum creatinine, and positive nitrites were found more often in culture-positive patients than in culture-negative pyuric patients [37].

Virulence

Escherichia coli (*E. coli*) was the most common organism followed by *Klebsiella*, *Proteus*, and *Pseudomonas*. Most of the urinary isolates were sensitive to ciprofloxacin, cotrimoxazole, and ceftriaxone, whereas resistance was high for ampicillin [10]. In a case-control study that profiled diabetic versus non-diabetic UTI, the prevalence of pyelonephritis was significantly higher in the diabetic subjects. Additionally, 87.14 % of the diabetics with UTI had glycosylated hemoglobin (HbA1c)>6.5 %. Isolation of microbes from urine cultures included *E. coli* at the highest rate of 64.6 %, followed by *Klebsiella* (12.1 %) and *Enterococcus* (9.9 %) in diabetics. *E. coli* showed maximum sensitivity to carbapenems in both diabetic and non-diabetic subjects and least susceptibility to ampicillin [34•]. In a comparison of clinical outcomes of UTI, patients with extended-spectrum, β-lactamase-producing *Escherichia coli* and *Klebsiella* species (ESBL-EK) versus patients with non-ESBL-EK UTIs were more likely to have DM [38•]. Awani et al. also found the prevalence of ESBL *E. coli* to be significantly higher in diabetics [34•].

Non-infectious Cystitis

Non-infectious or non-bacterial cystitis encompasses inflammatory processes that are less common, such as painful bladder syndrome (PBS), previously known as interstitial cystitis. Although recent publications exist on the topic of PBS in DM, none were published within the inclusion criteria dates. One case report discussed an 86-year-old woman with type II diabetes who was admitted due to lethargy and hyperglycemia, and was noted to have a tender and tympanic bladder upon exam. The computed tomography (CT) scan revealed distention with gas locules in the bladder wall. The authors diagnosed her with hyperglycemic, hyperosmolar non-ketosis precipitated by emphysematous cystitis. After treatment with systemic antibiotics and urethral catheter bladder drainage, her symptoms improved. The authors mention that surgical debridement and even cystectomy would only rarely be required [40].

Updates in DM and Bladder Dysfunction

Researchers have viewed the temporal impact of diabetic cystopathy as a progression from detrusor overactivity in the early stage of DM to bladder decompensation in the later stages. A prospective study followed the UDS of women in the early stages of type II DM and found that a subgroup with detrusor overactivity demonstrated impaired storage and emptying functions. The authors concluded that diabetes can presumably induce peripheral detrusor overactivity as a response to the impaired bladder contractility of DM [41]. A translational review summarized these findings; in contrast to a traditional concept of diabetic bladder dysfunction as a voiding problem characterized by poor emptying and overflow incontinence, a paradigm shift is seen in the clinical and experimental evidence indicating early-phase DM bladder compensation and late-phase decompensation. This temporal theory could possibly provide more scientific links to understanding the mechanisms of polyuria, hyperglycemia, oxidative stress, autonomic neuropathy, and decompensation of the bladder contractile apparatus in the manifestations of diabetic bladder dysfunction [21].

DM and SUI

Stress Urinary Incontinence (SUI)

A cross-sectional survey study of Jordanian women aged 20–65 years old queried 435 (43 %) diabetic and 576 (57 %) non-diabetic women. A total of 676 (66.8 %) women reported urinary incontinence. The prevalence of weekly or more frequent urge and stress incontinence was significantly higher in diabetic than in non-diabetic women, at 20 versus 14.2 %, respectively. After adjusting for age, body mass index, parity, and history of urinary tract infections in multiple logistic regression analyses, diabetes was significantly associated with any (OR: 1.99; 95 % CI: 1.44–2.74), urge (OR: 2.23; 95 % CI: 1.38–3.61), and stress incontinence (OR: 1.54; 95 % CI: 1.07–2.22). Women with incontinence perceived it as a bothersome condition with a negative impact on social well-being [14]. Regarding SUI treatment, diabetes was found to be a significant baseline characteristic associated with reduced satisfaction in patients receiving midurethral slings [42].

Novel UTI Pharmacotherapies in the Context of DM

With the goal of improved glycemic control, studies have evaluated LUTS improvement in diabetics treated with glycemic control agents. Dapagliflozin, an investigative SGLT2 inhibitor (which functions to increase the excretion of glucose into the urine) demonstrating glycemic benefits in type II DM patients

underwent a multi-trial safety data analysis to clarify the association between glucosuria and UTI. During phase III trials, a once-daily dose of 5 or 10 mg of dapagliflozin was accompanied by a slightly increased and not dose-dependent risk of UTI and no evidence of increase in pyelonephritis. Given the mild, uncomplicated, and clinically manageable nature of the UTIs, the authors concluded that these infections were considered typical for patients with type II diabetes. They generally did not lead to the discontinuation of treatment, and recurrence was uncommon [39]. Another SGLT2 inhibitor, Canagliflozin, was tested in a randomized, double-blind, placebo-controlled, multicenter, dose-ranging phase II study involving subjects with type II diabetes. The design involved seven arms incorporating other glycemic control agents. When compared with control subjects, canagliflozin increased urinary excretion of glucose, but was not associated with increased bacteriuria or UTI [43].

Novel Therapies and Techniques in Bladder Dysfunction Within the Context of DM

In a comparison of diabetics (mostly type II) and non-diabetics undergoing anticholinergic therapy for OAB with darifenacin, the presence of diabetes was associated with a significantly smaller reduction of OAB symptoms, but the effect attributable to diabetes was small relative to the overall treatment response by regression analysis. The only muscarinic receptor antagonist utilized in this study was darifenacin. The authors concluded that darifenacin has comparable efficacy and tolerability in the treatment of OAB patients with and without concomitant diabetes, but this conclusion cannot be generalized to all anticholinergics [40].

Uzun et al. compared anterior bladder wall thickness by ultrasound among women without overactive bladder (OAB), non-diabetic women with idiopathic OAB, and diabetic women with OAB. The results showed that women with OAB had significantly greater anterior bladder wall thickness compared to those without OAB, regardless of a history of DM or not. Women with diabetes but without OAB had greater (but not significant) bladder wall thickness than the controls [44]. While the authors located a notable finding on imaging, the clinical contribution is low, given that OAB and symptoms of urge can be easily discerned by history and urodynamics. Workup of this diagnosis rarely necessitates a bladder ultrasound.

Other Therapies

Stem Cell Application

A review of stem cell (SC) therapy for the bladder summarized that stem cell therapy studies for bladder dysfunction have been limited to an experimental basis and have been less focused than bladder regeneration. Adipose, bone marrow, and skeletal muscle-derived stem cells are used in transplantation to treat bladder dysfunction. The main mechanisms of stem cells to reconstitute or restore bladder dysfunction are migration, differentiation, and paracrine effects. Improved voiding function was noted in adipose-derived SC-treated rats as compared with phosphate-buffered saline-treated rats in an experimental model that involved a hypocontractile bladder pattern. This study showed some that adipose-derived SCs differentiated into smooth muscle cells, but that the paracrine pathway seems to play a main role in this process as well, suggesting that transplantation of adipose-derived SCs could result in the reduction of apoptosis and the preservation of the suburothelial capillaries network. Human studies involving the application of stem cells are limited to the neobladder and the urethral sphincter [22••].

Summarized Findings and Developments Among the Most Significant Recent Publications (See Annotated References)

- Novel therapies (including stem cells) targeting glycemic control and diabetic bladder dysfunction are showing encouraging results.
- The presence of severe nocturia in diabetic patients warrants careful surveillance for cardiovascular risk factors.
- Diabetics appear to be at higher risk for the most virulent strains of the common UTI microbes, so continued research on therapies against these strains is warranted.

Conclusion

From the most current publications studying LUTS in diabetic women, several conclusions can be drawn. Diabetes is a significant risk factor for dissatisfaction with treatment for SUI in women undergoing midurethral slings. Aging and obesity are significantly and reliably associated with worsened LUTS in diabetic women. Glucosuria has a varying effect on urodynamic parameters and LUTS, but a significant association with UTI and incontinence at clinically relevant numbers, such as HbA1C values. Antimuscarinic therapy for OAB in diabetics continues to show satisfactory results. The presence of severe nocturia in diabetic patients warrants careful surveillance for cardiovascular risk factors.

The most common microbes responsible for UTIs in the diabetic population mirror those in the general population, although diabetics appear to be at higher risk for colonization with the virulent, extended-spectrum, β-lactamase-producing *Escherichia coli* and *Klebsiella* species. Although having

received prior attention, current studies are lacking in discussion of the relationships between PBS and DM.

Novel therapies for diabetic neurogenic bladder are undergoing trials in animal models with promising functional results. Investigative SGLT2 inhibitors for glycemic control have demonstrated encouraging results in the role of diabetes therapy given that increased glucosuria continues to be linked with only insignificant to minimal numbers of UTI in current trials. Stem cell therapy appears to have the most promising projection for future LUTS therapies, but focused efforts must be made to conduct human studies.

Discussion

Given the high frequency of midurethral sling placement for the treatment of SUI, as well as the growing numbers of diabetic women in the population, mindfulness must be considered and adequate counseling held between the patient and her provider regarding diabetes as a significant risk factor for decreased satisfaction after sling placement.

The alarming significance between nocturia of ≥3 times per night and cardiovascular mortality in diabetic patients warrants urging the patient to maintain vigilant surveillance with her primary care provider in routine cardiovascular risk screenings. In a sense, the symptom of nocturia may prove to be a valuable warning sign in the care of diabetic patients.

Further investigations of the SGLT2 inhibitors for glycemic control will be interesting to follow as studies enroll larger numbers of patients and further delineate the medication safety and any associations with UTI.

The findings of generalized LUTS remain mixed in the relationships between levels of glucosuria and LUTS, in that PVR is increased, but urge incontinence is not. Studies have suggested that certain magnitudes of glycemic control may impact whether LUTS such as incontinence and UTI will arise. The utilization of certain mechanisms to lower blood glucose by increasing urinary excretion has resulted in expected increases in glucosuria, but thus far only shows mild to no increases in UTI.

An attached algorithm is included to remind care providers about the significant findings from the most recent publications in the treatment of their DM patients with LUTS (See Fig. 1).

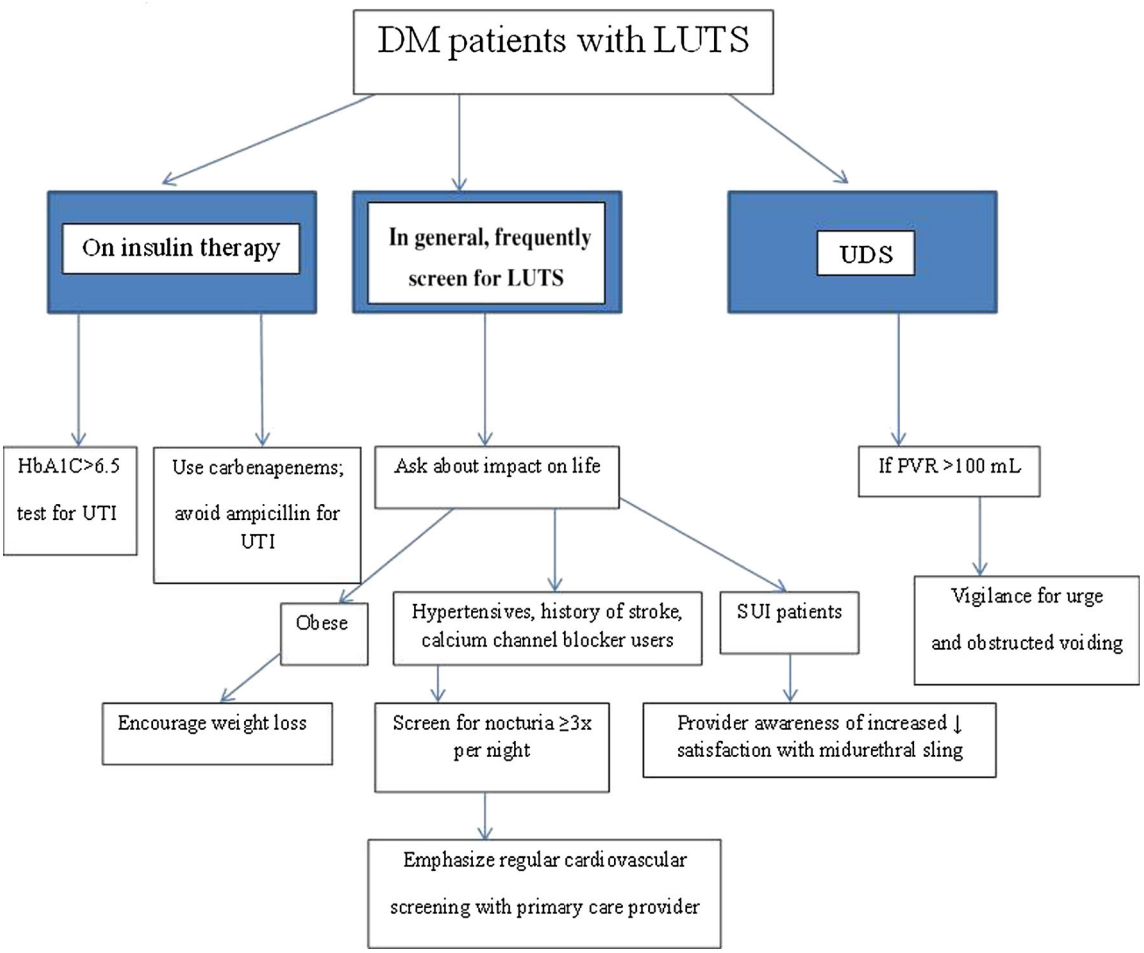

Fig. 1 Algorithm for care providers of diabetic women

Compliance with Ethics Guidelines

Conflict of Interest Dr. Rebecca James and Dr. Adonis Hijaz each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Samsioe G, Heraib F, Lidfeldt J, et al. Urogenital symptoms in women aged 50-59 years. Women's Health in Lund Area (WHILSA) Study Group. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 1999;13(2):113–7.
2. 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(5 Pt 1):715–21.
3. Farrell SA, Allen VM, Baskett TF. Parturition and urinary incontinence in primiparas. Obstet Gynecol. 2001;97(3):350–6.
4. Brown JS, Vittinghoff E, Lin F, Nyberg LM, Kusek JW, Kanaya AM. Prevalence and risk factors for urinary incontinence in women with type 2 diabetes and impaired fasting glucose: findings from the National Health and Nutrition Examination Survey (NHANES) 2001-2002. Diabetes Care. 2006;29(6):1307–12.
5. Brown JS, Wing R, Barrett-Connor E, et al. Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. Diabetes Care. 2006;29(2):385–90.
6. Foldspang A, Hvidman L, Mommsen S, Nielsen JB. Risk of postpartum urinary incontinence associated with pregnancy and mode of delivery. Acta Obstet Gynecol Scand. 2004;83(10):923–7.
7. Ebbesen MH, Hannestad YS, Midthjell K, Hunskaar S. Diabetes and urinary incontinence - prevalence data from Norway. Acta Obstet Gynecol Scand. 2007;86(10):1256–62.
8. Danforth KN, Townsend MK, Lifford K, Curhan GC, Resnick NM, Grodstein F. Risk factors for urinary incontinence among middle-aged women. Am J Obstet Gynecol. 2006;194(2):339–45.
9. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. Diabetologia. 2007;50(3):549–54.
10. Simkhada R. Urinary tract infection and antibiotic sensitivity pattern among diabetics. Nepal Med Coll J NMCJ. 2013;15(1):1–4.
11. Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin N Am. 1997;11(3):735–50.
12. Kesah CN, Coker AO, Alabi SA, Olukoya DK. Prevalence, antimicrobial properties and beta-lactamase production of haemolytic enterobacteria in patients with diarrhoea and urinary tract infections in Legos, Nigeria. Cent Afr J Med. 1996;42(5):147–50.
13. Muller LM, Gorter KJ, Hak E, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005;41(3):281–8.
14. Bani-Issa W, Almomani F, Eldeirawi K. Urinary incontinence among adult women with diabetes in Jordan: epidemiology, correlates and perceived impact on emotional and social well-being. J Clin Nurs. 2013.
15. Palleschi G, Pastore AL, Maggioni C, et al. Overactive bladder in diabetes mellitus patients: a questionnaire-based observational investigation. World J Urol. 2013.
16. Ahmed HM, Osman VA, Al-Alaf SK, Al-Tawil NG. Prevalence of urinary incontinence and probable risk factors in a sample of kurdish women. Sultan Qaboos Univ Med J. 2013;13(2):269–74.
17. Appa AA, Brown JS, Creasman J, et al. Clinical predictors and significance of postvoid residual volume in women with diabetes. Diabetes Res Clin Pract. 2013;101(2):164–9.
18. •• Chung MS, Chuang YC, Lee JJ, Lee WC, Chancellor MB, Liu RT. Prevalence and associated risk factors of nocturia and subsequent mortality in 1,301 patients with type 2 diabetes. Int Urol Nephrol. 2014. *The alarming significance between nocturia of≥3 times per night and cardiovascular mortality in diabetic patients warrants a provider to urge the patient to maintain vigilant surveillance with her primary care provider in routine cardiovascular risk screenings. In a sense, the symptom of nocturia may prove to be a valuable warning in the care of diabetic patients.*
19. Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267–80.
20. Lee WC, Wu HC, Huang KH, Wu HP, Yu HJ, Wu CC. Hyposensitivity of C-fiber afferents at the distal extremities as an indicator of early stages diabetic bladder dysfunction in type 2 diabetic women. PLoS One. 2014;9(1):e86463.
21. Kirschner-Hermanns R, Daneshgari F, Vahabi B, Birder L, Oelke M, Chacko S. Does diabetes mellitus-induced bladder remodeling affect lower urinary tract function? ICI-RS 2011. Neurourol Urodyn. 2012;31(3):359–64.
22. •• Kim JH, Lee SR, Song YS, Lee HJ. Stem cell therapy in bladder dysfunction: where are we? And where do we have to go? BioMed Res Int. 2013;2013:930713. *Stem cell therapy appears to have the most promising projection for future LUTS therapies, but focused efforts must be made to conduct human studies*.
23. Daneshgari F, Liu G, Imrey PB. Time dependent changes in diabetic cystopathy in rats include compensated and decompensated bladder function. J Urol. 2006;176(1):380–6.
24. 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(6):R1728–35.
25. Hammar N, Farahmand B, Gran M, Joelson S, Andersson SW. Incidence of urinary tract infection in patients with type 2 diabetes. Experience from adverse event reporting in clinical trials. Pharmacoepidemiol Drug Saf. 2010;19(12):1287–92.
26. Kullmann FA, Wells GI, McKenna D, Thor KB. Excitatory effects of bombesin receptors in urinary tract of normal and diabetic rats in vivo. Life Sci. 2014;100(1):35–44.
27. Ren LM, Zhuo YJ, Hao ZS, He HM, Lu HG, Zhao D. Berberine improves neurogenic contractile response of bladder detrusor muscle in streptozotocin-induced diabetic rats. J Ethnopharmacol. 2013;150(3):1128–36.
28. Changxiao H, Zhengyong Y, Shibing Y, et al. Clinical and urodynamic evaluation of women referred with diabetes mellitus. Int Urogynecol J. 2014.
29. Ding L, Song T, Yi C, et al. Transcutaneous electrical nerve stimulation (TENS) improves the diabetic cytopathy (DCP) via up-regulation of CGRP and cAMP. PLoS One. 2013;8(2):e57477.
30. Kaplan SA, Te AE, Blaivas JG. Urodynamic findings in patients with diabetic cystopathy. J Urol. 1995;153(2):342–4.
31. Starer P, Libow L. Cystometric evaluation of bladder dysfunction in elderly diabetic patients. Arch Intern Med. 1990;150(4):810–3.

32. Chang TC, Chang SR, Hsiao SM, Hsiao CF, Chen CH, Lin HH. Factors associated with fecal incontinence in women with lower urinary tract symptoms. J Obstet Gynaecol Res. 2013;39(1):250–5.
33. Stav K, Shilo Y, Zisman A, Lindner A, Leibovici D. Comparison of lower urinary tract symptoms between women with detrusor overactivity and impaired contractility, and detrusor overactivity and preserved contractility. J Urol. 2013;189(6):2175–8.
34.• Aswani SM, Chandrashekar U, Shivashankara K, Pruthvi B. Clinical profile of urinary tract infections in diabetics and non-diabetics. Australas Med J. 2014;7(1):29–34. *The above study discusses how diabetics appear to be at higher risk for the most virulent strains of the common UTI microbes (extended-spectrum, β-lactamase-producing Escherichia coli and Klebsiella species; ESBL-EK), so continued research in therapies against these strains is warranted. E. coli has shown maximum sensitivity to carbapenems and the least susceptibility to ampicillin*.
35. Mody L, Juthani-Mehta M. Urinary tract infections in older women: a clinical review. JAMA J Am Med Assoc. 2014;311(8):844–54.
36. Tsai SW, Kung FT, Chuang FC, Ou YC, Wu CJ, Huang KH. Evaluation of the relationship between urodynamic examination and urinary tract infection based on urinalysis results. Taiwan J Obstet Gynecol. 2013;52(4):493–7.
37. Mamun Mahmud H, Qureshi S, Kumar D, Farman S. Pyuric diabetic patients: a tertiary centre experience from Karachi. Pak J Med Sci. 2014;30(1):77–80.
38.• Macvane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum beta-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med Off Publ Soc Hosp Med. 2014;9(4):232–8. *The above study discusses how diabetics appear to be at higher risk for the most virulent strains of the common UTI microbes (extended-spectrum, β-lactamase-producing Escherichia coli and Klebsiella species; ESBL-EK), so continued research in therapies against these strains is warranted. E. coli has shown maximum sensitivity to carbapenems and the least susceptibility to ampicillin*.
39. Johnsson KM, Ptaszynska A, Schmitz B, Sugg J, Parikh SJ, List JF. Urinary tract infections in patients with diabetes treated with dapagliflozin. J Diabetes Complicat. 2013;27(5):473–8.
40. Dixon L, Winkler M. Emphysematous cystitis: a tympanic bladder. BMJ Case Rep. 2013;2013.
41. 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(2):R84–93.
42. Wai CY, Curto TM, Zyczynski HM, et al. Patient satisfaction after midurethral sling surgery for stress urinary incontinence. Obstet Gynecol. 2013;121(5):1009–16.
43. Nicolle LE, Capuano G, Ways K, Usiskin K. Effect of canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, on bacteriuria and urinary tract infection in subjects with type 2 diabetes enrolled in a 12-week, phase 2 study. Curr Med Res Opin. 2012;28(7):1167–71.
44. Uzun H, Ogullar S, Sahin SB, et al. Increased bladder wall thickness in diabetic and nondiabetic women with overactive bladder. Int Neurourol J. 2013;17(2):67–72.