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OVERACTIVE BLADDER (U LEE AND S ADELSTEIN, SECTION EDITORS)

Overactive Bladder in Diabetes Mellitus

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Abstract

Purpose of Review To explore the current literature regarding the epidemiology, pathophysiology, diagnosis, and management of overactive bladder in diabetic patients.

Recent Findings Overactive bladder is a syndrome complex of urinary urgency, often accompanied by frequency and nocturia. Several studies have established the relationship between diabetes mellitus and bladder dysfunction. However, there is limited literature available to evaluate the prevalence of overactive bladder in this population and to guide clinical practice. The introduction of medications such as mirabegron and minimally invasive techniques such as intravesicular onabotulinumtoxinA injections has resulted in a shift in the treatment model for overactive bladder. New technologies for treatment such as radiofrequency therapy are also under active development. Ongoing research seeks to further understand the mechanisms involved in the pathogenesis of overactive bladder and identify biomarkers.

Summary With the increasing prevalence of diabetes mellitus, it is expected that patients with overactive bladder symptoms will be seen more frequently. The American Urological Association (AUA) and Society of Urodynamics and the Female Pelvic Medicine & Urogenital Reconstruction (SUFU) recently updated the guidelines for the diagnosis for overactive bladder in 2019. However, there are important considerations in diabetic patients that may alter clinical evaluation and management. We tried to shed some light on these diagnostic considerations and the management options available to diabetic patients.

Keywords Overactive bladder · Diabetes mellitus · Incontinence · Urinary tract infection

Abbreviations

DM	diabetes mellitus
US	United States
LUTS	lower urinary tract symptoms
BPH	benign prostatic hyperplasia
OAB	overactive bladder
UTI	urinary tract infection
ER	endoplasmic reticulum
AUA	American Urological Association
SUFU	Female Pelvic Medicine & Urogenital Reconstruction
PCP	primary care physician
PTNS	peripheral tibial nerve stimulation

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Introduction

The prevalence of both type 1 and type 2 diabetes mellitus (DM) is predicted to increase by 54% in the United States (US) between the years 2015 and 2030 [1]. DM often results in serious morbidity affecting multiple organ symptoms, including the lower urinary tract. In fact, lower urinary tract symptoms (LUTS) affect up to 80% of patients with DM [2, 3]. DM impacts the lower urinary tract by several mechanisms: chronic hyperglycemia causes polyuria and can lead to peripheral nerve injury and neuropathy, which subsequently results in dysregulation of myogenic and neurogenic components of micturition. Additionally, conditions associated with DM, such as obesity and metabolic syndrome, also disrupt normal lower urinary tract function [4]. While the effects of

DM on the lower urinary tract have long been acknowledged, there is a relative paucity of literature on this topic.

Few studies have reviewed the epidemiology and pathophysiology of the relationship between overactive bladder and DM, and there is limited research available to guide clinical practice. In addition, most studies have focused on women as they tend to have a higher rate of urinary incontinence. Research in men is complicated by conditions such as benign prostatic hyperplasia (BPH) that may present with LUTS similar to those experienced as a result of DM, thus serving as a significant confounder. However, bladder changes with DM are prevalent in both men and women and have a significant impact on the quality of life in both groups.

In this review, we focus on one of the most common urological complications: overactive bladder (OAB). OAB is defined as a syndrome of urinary urgency, often accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other underlying pathology [5]. We discuss the epidemiology, current understanding of the pathophysiology, diagnosis, and management of OAB in diabetic patients. We hope the information presented will aid both primary care physicians and urologists in providing optimal care of these patients.

Epidemiology

Numerous studies have been conducted to identify the prevalence of OAB. Data on the overall prevalence of OAB is variable, with this condition estimated to affect 11.8% to 35.6% of the general population, though most published literature indicates a higher prevalence in women than men [6–10].

In the US, the National Overactive Bladder Evaluation (NOBLE) study in 2003 found the prevalence of OAB to be similar in women and men (16.9% and 16%, respectively) [6]. The Epidemiology of Lower Urinary Tract Symptoms (EpiLUTS) study found the prevalence of OAB in women and men to be 43.1% and 27.2%, respectively, and reported that approximately 29.8 million adults in the US aged ≥ 40 years had bothersome OAB symptoms [7]. The international multicenter EPIC study, including data from Canada, Germany, Italy, Sweden, and the United Kingdom found an overall prevalence of 11.8%, with similar rates in women and men (12.8% and 10.8%) [8]. Finally, the Milsom study which was conducted in six European countries found the overall prevalence of OAB to be 16.6% with the prevalence among women and men as 17.4% and 15.6% [9].

The available literature addressing the prevalence of OAB in patients with DM is limited. A questionnaire-based study conducted by Palleschi et al. (2014) in Italy found that OAB was more common in diabetic patients (35.7% of DM group vs. 4.8% of control group). Among the diabetic patients, the prevalence of OAB among women and men was found to be 36.1% and 34.9%, respectively [11]. Liu et al. (2011) queried patients at a dedicated diabetic center in Taiwan. Among patients with type 2 diabetes, 22.5% had OAB, including 20.1% of women and 24.8% of men [12]. Finally, a more recent study conducted by Xu et al. (2017) in mainland China found the prevalence of OAB in patients with type 2 diabetes to be 13.9%, which is two-fold greater than that in the Chinese general population [13]. Although population-level data in patients with DM is scarce, published data indicates that the burden of OAB symptoms is significantly greater among diabetic patients, with nearly double the prevalence in this unique population.

Pathogenesis of Overactive Bladder in Diabetes Mellitus

The bladder is composed of several layers, all of which undergo changes as a result of diabetes. The innermost layer is the urothelium; it acts as a non-permeable barrier and prevents leakage of urine, thereby protecting the underlying tissue. The urothelium has chemical, mechanical, and thermal sensors which relay the extent of bladder fullness to the neurogenic and myogenic systems [14]. The next layer is the lamina propria which connects the urothelium layer to the underlying smooth muscle. It contains collagen, interstitial cells, fibroblasts, adipocytes, abundant blood supply, and nerve bundles. This is followed by three layers of detrusor smooth muscle that operate under sympathetic and parasympathetic control. The detrusor muscle is composed of an inner layer with circular muscle fibers sandwiched between two layers of longitudinal smooth muscle. Finally, the urethra is responsible for voiding the bladder and is held by the internal urethral sphincter made of smooth muscle and the external urethral sphincter made of skeletal muscle [15].

There are several studies in the literature with suggested mechanisms to describe the changes occurring due to diabetes in all the layers of the bladder in a time-dependent manner. Studies have demonstrated changes in muscle contractility due to calcium homeostasis, ion channels and receptors, oxidative stress, neuropathy, inflammation, cellular senescence, alterations in urothelial mechanosensitivity and cell signaling [15–20]. Wang et al. (2017) observed structural changes involving the endoplasmic reticulum (ER) cisternae in streptozotocin-induced diabetic rats. They observed swelling, fusion, and degranulation of cisternae in the ER, deformed nuclei and increased apoptosis in the detrusor smooth muscle after the 12th week of induction. These findings may add ER stress to the complex picture in the pathogenesis of bladder dysfunction in diabetes [21]. An early study by Daneshgari et al. (2006) analyzed streptozotocin-induced diabetic rats and developed a temporal model of an early compensated to a late

decompensated bladder state. It was found that morphological damage to the detrusor smooth muscle begins 9–12 weeks after induction and is characterized with the progressive loosening and collapse of muscle bundles under light microscopy [22].

The temporal hypothesis proposed by Daneshgari et al. [2, 22] describes a spectrum of clinical presentation and urodynamic findings. The initial stage is an early compensated state which results from hyperglycemia coupled with osmotic diuresis and polyuria. The patient at this stage will experience bladder storage problems and may clinically present with urgency, increased urinary frequency, and nocturia. The early stage may then progress to a late decompensated state which results from a chronic hyperglycemic state coupled with oxidative stress. The patient in the late decompensated state is characterized by voiding difficulties and may present with underactive bladder, reduced bladder contractility, and difficulty initiating and maintaining a urine stream with increased post-void residual volume and overall capacity. The clinical findings in a patient with DM, therefore, range from increased bladder contractility to impaired contractility which may progress further to flaccidity and impact the upper tract with recurrent pyelonephritis and kidney failure [22].

Diagnosis

The 2019 American Urological Association (AUA) and Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) guidelines for the diagnosis for OAB recommends a thorough diagnostic process which includes, at a minimum, a careful history, physical exam, and urinalysis in all patients [23••]. Bladder symptoms should be carefully documented along with baseline symptoms, duration, and medical comorbidities. The degree of bother is a key clinical parameter which must be assessed as it is unnecessary to begin treatment in patients who are not bothered by LUTS. For the diabetic patient under the care of a primary care physician (PCP), bladder symptoms should be carefully documented along with baseline symptoms, duration, and comorbidities to determine whether the patient requires referral to a urologist. In addition to DM, relevant comorbidities in a complicated patient may include stroke, spinal cord injury, multiple sclerosis, motility disorders, chronic pelvic pain, recurrent urinary tract infections, prior pelvic surgeries, pelvic cancer, and pelvic radiation [23••].

In a diabetic patient, one may consider additional diagnostic procedures typically reserved for a complex presentation, including a post-void residual and urodynamics. Though the AUA/SUFU recommends against urodynamics, cystoscopy, and renal/bladder ultrasound for uncomplicated patients [23••], patients with DM have variable phenotypes of bladder dysfunction that may warrant this additional testing. If the patient has not undergone testing within 3 months, a hemoglobin A1c should also be included in the initial evaluation, particularly if there is an acute onset or change in symptoms, which may indicate worsening hyperglycemia. The rate of infections is also higher in diabetic patients; hence, urinalysis and urine culture with additional tests to assess the degree of glycemic control may be necessary [24].

It is also important to keep in mind that a patient presenting with OAB symptoms may have underlying undiagnosed DM. Therefore, it is imperative to conduct a thorough exam which includes evaluation for signs of DM, such as acanthosis nigricans, truncal obesity, weight changes, and vision changes. Glucosuria on urinalysis may also indicate a diagnosis of DM. Medications taken by the patient should be reviewed since several medications used for glycemic control such as SGLT-2 inhibitors induce glycosuria. Diuretics also increase urine output and may precipitate symptoms. Diagnosis of DM may be confirmed with hemoglobin A1C values, a fasting glucose test or a two-hour glucose test.

Management

Management should be tailored to each individual patient, taking into account symptom severity and goals of treatment.

Patient Education Thorough patient and caregiver counseling is the foundation of OAB treatment. It is very important for the patient to understand that OAB associated with diabetes is a symptom complex with a chronic and progressive course. Therefore, the patient's active participation is important for successful treatment. Substantial improvements can be achieved by actively partnering with the patient and PCP for glycemic control and weight management. A qualitative study by Davenport et al. (2019) found that insufficient in-office education was a common barrier to transitioning to third-line therapy [25•]. Education about the OAB clinical care pathway which was created from the guidelines set by AUA and SUFU will aid in expectation management and ease the transition to advanced therapy in patients who develop refractory symptoms. The clinical care pathway is available for free at www.SUFUorg.com.

Lifestyle and Behavioral Modifications Lifestyle modifications include weight loss, diet changes, and behavioral therapies include bladder training, bladder control techniques, fluid intake management, and pelvic floor muscle strengthening. These techniques can significantly help with symptom improvement in diabetic patients [26].

Weight loss has long been established to be highly effective in reducing the risk of diabetes and preventing complications [27]. An incontinence sub-study from the results of the Diabetes Prevention Program Outcomes study, which

investigated the persistence of positive effects from lifestyle interventions and metformin, found that intensive lifestyle interventions have a positive and enduring impact on urinary continence. The prevalence of weekly incontinence was lower in the intensive lifestyle intervention group when compared to the metformin and placebo groups (44.2% vs. 51.8%, 48.0% urinary incontinence/week) [28]. A strong emphasis on glycemic control, blood pressure control, and smoking cessation are other important components in the management of diabetic patients.

A bladder diary to document fluid intake and voiding behavior is a first step to identify targets for individualized behavioral management goals. Repeat bladder diaries may then be used to monitor progress and evaluate treatment efficacy. The PCP can partner with patients and caregivers to make small adjustments to daily routines such as timed voiding, voiding before bed-time, limiting fluid intake, and avoiding food or beverages which may irritate the bladder.

Pelvic floor muscle exercises may also alleviate OAB symptoms, with efficacy supported by systematic meta-analysis [29]. Referral to a physical therapist specializing in pelvic floor therapy may be offered as part of any conservative management plan.

Pharmacologic Management Oral anti-muscarinic medications (e.g., oxybutynin, solifenacin, tolterodine) or oral β_3-adrenoceptor agonists (mirabegron) may be offered as second-line therapy following failure of or in conjunction with lifestyle and behavioral adjustments.

There are several possible side effects of anti-muscarinics, most notably dry mouth, dry eyes, and constipation. In addition, muscarinic blockade in the brain may result in cognitive impairment and the development of dementia especially in middle-aged and older people [30•]. Diabetic patients, in particular, are prone to cognitive decline which may be accelerated when treated with anti-muscarinics. Data from the Taiwan National Health Insurance Research Database suggests that rates of dementia were significantly higher in diabetic patients taking oxybutynin, solifenacin, and tolterodine (3.9%, 4.3%, and 2.2%, respectively) compared to diabetic patients not taking anti-muscarinic medications (1.2%) [31]. Given the potential association with dementia, cognitive impairment must be assessed prior to initiating therapy or transitioning to the next level of therapy. It may be beneficial to use anti-muscarinics that have more favorable properties with regard to side effects that effect the brain and cognitive function. These include trospium, tolterodine, darifenacin, and solifenacin [32].

β_3-adrenoceptor agonists such as mirabegron may be the preferred drug in patients who may need to avoid anti-muscarinics or may be already taking a cholinesterase inhibitor. The main concerns with mirabegron are the effect on the cardiovascular system due to the presence of these receptors in those tissues. Hypertension may develop as a result of treatment and hence blood pressure will need to be monitored closely.

The SYNERGY II study evaluated the long-term safety and efficacy of combination therapy of mirabegron and solifenacin versus monotherapy for overactive bladder (OAB) in 2018. They reported only a slightly higher frequency of adverse events from combination therapy when compared to mirabegron and solifenacin alone (49% versus 41% versus 44%, respectively) [33•].

Minimally Invasive and Surgical Techniques Peripheral tibial nerve stimulation (PTNS), sacral neuromodulation, and intradetrusor onabotulinumtoxinA injection may be offered as third-line therapies when both behavioral and pharmacological management are ineffective for the patient.

PTNS is carried out by stimulating the S3 sacral nerve plexus, using a retrograde pathway via direct stimulation of the posterior tibial nerve. PTNS is a simple outpatient procedure and an attractive option for patients who cannot tolerate the side effects of medications. Several studies have demonstrated the efficacy of PTNS in improving OAB symptoms. In trials comparing PTNS to anti-muscarinic drugs, the symptomatic improvements were similar and side effect profiles were superior [34–36]. A single-center study conducted by Mathieu et al. (2017) addressed PTNS outcomes in patients with and without DM and found similar functional outcomes in both diabetic and non-diabetic groups [37]. Considering the side effects of medical management and polypharmacy experienced by many, PTNS may be more desirable for certain patients.

Cystoscopic injection of onabotulinumtoxinA into the detrusor muscle works by inhibiting the release of acetylcholine at the neuromuscular junction in peripheral nerve endings resulting in temporary muscle paralysis. Studies indicate that onabotulinumtoxinA injections can improve symptoms in patients with moderate to severe OAB symptoms [38–41]. Wang et al. (2014) evaluated the safety and efficacy of intravesicular onabotulinumtoxinA injection in patients with DM and OAB. They reported success rates that were statistically similar in both the DM and control groups (56% and 61%, respectively) [42]. After intravesical onabotulinumtoxinA injection, the rate of transient urinary retention in the general population was found to be 35% [43]. The DM patients in the same study by Wang et al. had significantly higher larger post-void residual volumes compared to the control group (60.4% and 33.3%, respectively) as well as general weakness (10.4% and 0%, respectively) [42]. Patients with DM, then, should be counseled about a higher than normal risk of post-procedure urinary retention that may require intermittent self catheterization.

Sacral neuromodulation is another surgical treatment option in carefully selected patients. This device delivers mild electrical impulses to the sacral nerve roots using an implanted neurostimulator and lead and is usually placed adjacent to the S3 sacral nerve root. There are several considerations prior to

device implantation. Patients must have the cognitive and motor ability to operate the remote control of the neurostimulator, the battery or device itself may need periodic surgical replacement, and patients with implanted devices cannot undergo MRIs, though newer devices in product development are MRI compatible. Studies have also reported frequent adverse events such as pain or electric shock sensation at the device site, lead migration, need for surgical correction, infection at site of implantation [44–48]. Infection risk is of particular concern in patients with DM. In fact, Daniel et al. (2010) conducted a study on patients undergoing sacral neurostimulator implantation. While success rate was similar in both the diabetic and non-diabetic cohorts, the number of device removals due to infections was higher in the diabetic cohort (37.5 vs. 25.5%) [24, 49].

Conclusions and Future Directions

OAB is a common pathology reported in 11.8% to 35.6% of patients in the general population [6–10]. Patients with DM experience more severe symptoms, with a higher impact on their quality of life. It is important for providers to recognize the synergistic effect of DM on patients with OAB and manage these patients with consideration for their increased risk of urinary tract infection and their likelihood of failing primary and secondary therapies.

The precise mechanisms involved in the pathogenesis of OAB in a diabetes bladder remain to be fully understood. Studying the molecular mechanisms may help with the development of better diagnostic tools and treatment options. There are promising efforts being made investigate biomarkers of OAB such as nerve growth factor, prostaglandin E2, adenosine triphosphate [50••, 51••]. The results from a recent study suggest that alteration of stable microRNA (miRNA) levels in plasma may be used as auxiliary parameters to evaluate the mechanisms involved in the pathophysiology of OAB [52].

Finally, there are new technologies for the treatment of OAB under active development. Radiofrequency therapy can be used to disrupt nerve signaling pathways within the bladder and there are a few studies being conducted to evaluate its safety and efficacy [53]. Another recent study developed an external compression-release protocol that was demonstrated in an ex *vivo* porcine model. The authors suggest that this technique could represent a noninvasive form of pelvic floor muscle therapy that could potentially decrease the load on bladder tension sensors and hence reduce urinary urgency [54].

Compliance with Ethical Standards

Conflict of Interest Adonis K Hijaz reports personal fees from Astellas, grants from Juventas Therapeutics, outside the submitted work. Vaishnavi Narayanamurthy, Emily A Slopnick, David D Sheyn, Laura Bukavina, and Kirtishri Mishra declare that they have no conflict 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. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: insights from yesterday, today, and Future trends. Popul Health Manag. 2017;20:6–12.
2. Daneshgari F, Liu G, Birder L, Hanna-Mitchell AT, Chacko S. Diabetic bladder dysfunction: current translational knowledge. J Urol. 2009;182:S18–26.
3. Daneshgari F, Moore C. Diabetic Uropathy. Semin Nephrol. 2006;26:182–5.
4. Daneshgari F, Liu G, Hanna-Mitchell AT. Path of translational discovery of urological complications of obesity and diabetes. Am J Physiol Physiol. 2017;312:F887–96.
5. Haylen BT, de Ridder D, Freeman RM, et al. An international urogynecological association (IUGA)/international continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2009;21:5–26.
6. Stewart W, van Rooyen J, Cundiff G, Abrams P, Herzog A, Corey R, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 20:327–36.
7. Coyne KS, Sexton CC, Vats V, Thompson C, Kopp ZS, Milsom I. National Community Prevalence of overactive bladder in the United States stratified by sex and age. Urology. 2011;77:1081–7.
8. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50:1306–15.
9. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int. 2001;87:760–6.
10. Eapen RS, Radomski SB. Gender differences in overactive bladder. Can J Urol. 2016;23:2–9.
11. Palleschi G, Pastore AL, Maggioni C, Fuschi A, Pacini L, Petrozza V, et al. Overactive bladder in diabetes mellitus patients: a questionnaire-based observational investigation. World J Urol. 2014;32:1021–5.
12. Liu R-T, Chung M-S, Lee W-C, Chang S-W, Huang S-T, Yang KD, et al. Prevalence of overactive bladder and associated risk factors in 1359 patients with type 2 diabetes. Urology. 2011;78:1040–5.
13. Xu D, Gao J, Wang X, Huang L, Wang K. Prevalence of overactive bladder and its impact on quality of life in 1025 patients with type 2 diabetes in mainland China. J Diabetes Complicat. 2017;31:1254–8.
14. Birder LA. Urinary bladder, cystitis and nerve/urothelial interactions. Auton Neurosci. 2014;182:89–94.
15. Klee NS, McCarthy CG, Lewis S, McKenzie JL, Vincent JE, Webb RC. Urothelial senescence in the pathophysiology of diabetic bladder dysfunction—a novel hypothesis. Front Surg. 2018;5:72.
16. Mustafa S. Effect of diabetes on the ion pumps of the bladder. Urology. 2013;81:211.e17–21.

17. Kendig DM, Ets HK, Moreland RS. Effect of type II diabetes on male rat bladder contractility. Am J Physiol Physiol. 2016;310: F909–22.
18. Inouye BM, Hughes FM Jr, Jin H, Lütolf R, Potnis KC, Routh JC, et al. Diabetic bladder dysfunction is associated with bladder inflammation triggered through hyperglycemia, not polyuria. Res Rep Urol. 2018;10:219–25.
19. Szasz T, Wenceslau CF, Burgess B, Nunes KP, Webb RC. Toll-like receptor 4 activation contributes to diabetic bladder dysfunction in a murine model of type 1 diabetes. Diabetes. 2016;65:3754–64.
20. Hanna-Mitchell AT, Ruiz GW, Daneshgari F, Liu G, Apodaca G, Birder LA. Impact of diabetes mellitus on bladder uroepithelial cells. Am J Physiol Integr Comp Physiol. 2013;304:R84–93.
21. Wang D, Yuan X, Hu C, Zhang B, Gao H, Wang D, et al. Endoplasmic reticulum stress is involved in apoptosis of detrusor muscle in streptozocin-induced diabetic rats. Neurourol Urodyn. 2017;36:65–72.
22. Daneshgari F, Liu G, Imrey PB. Time dependent changes in diabetic Cystopathy in rats include compensated and decompensated bladder function. J Urol. 2006;176:380–6.
23.•• Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. J Urol. 2019. https://doi.org/10.1097/JU.0000000000000309 **Updated AUA/SUFU guidelines for OAB.**
24. Abu-Ashour W, Twells LK, Valcour JE, Gamble J-M. Diabetes and the occurrence of infection in primary care: a matched cohort study. BMC Infect Dis. 2018;18:67.
25.• Davenport A, Stark S, Quian A, Sheyn D, Mangel J. A patient-centered approach to refractory overactive bladder and barriers to third-line therapy. Obstet Gynecol. 2019;134:141–8 **Importance of patient education in management and treatment compliance of OAB.**
26. Brown JS, Wing R, Barrett-Connor E, Nyberg LM, Kusek JW, Orchard TJ, et al. Lifestyle intervention is associated with lower prevalence of urinary incontinence: the diabetes prevention program. Diabetes Care. 2006;29:385–90.
27. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346: 393–403.
28. Phelan S, Kanaya AM, Ma Y, et al. Long-term prevalence and predictors of urinary incontinence among women in the diabetes prevention program outcomes study. Int J Urol. 2015;22:206–12.
29. Dumoulin C, Cacciari LP, Hay-Smith EJC. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2018;10:CD005654.
30.• Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia. JAMA Intern Med. 2019. https://doi.org/10.1001/jamainternmed.2019.0677 **Importance of minimizing treatment with anticholinergic medications in older patients.**
31. Yang Y-W, Liu H-H, Lin T-H, Chuang H-Y, Hsieh T. Association between different anticholinergic drugs and subsequent dementia risk in patients with diabetes mellitus. PLoS One. 2017;12: e0175335.
32. Cetinel B, Onal B. Rationale for the use of anticholinergic agents in overactive bladder with regard to central nervous system and cardiovascular system side effects. Korean J Urol. 2013;54:806–15.
33.• Gratzke C, van Maanen R, Chapple C, et al. Long-term safety and efficacy of Mirabegron and Solifenacin in combination compared with monotherapy in patients with overactive bladder: a randomised, multicentre phase 3 study (SYNERGY II). Eur Urol. 2018;74:501–9 **SYNERGY II trial demonstrated efficacy and safety of combination treament using Mirabegron and Solifenacin.**
34. Gaziev G, Topazio L, Iacovelli V, Asimakopoulos A, Di Santo A, De Nunzio C, et al. Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. BMC Urol. 2013;13:61.
35. Levin PJ, Wu JM, Kawasaki A, Weidner AC, Amundsen CL. The efficacy of posterior tibial nerve stimulation for the treatment of overactive bladder in women: a systematic review. Int Urogynecol J. 2012;23:1591–7.
36. Moossdorff-Steinhauser HFA, Berghmans B. Effects of percutaneous tibial nerve stimulation on adult patients with overactive bladder syndrome: a systematic review. Neurourol Urodyn. 2013;32: 206–14.
37. Mathieu L, Peyronnet B, Senal N, Fontaine S, Manunta A, Honoré T, et al. [outcomes of transcutaneous posterior tibial nerve stimulation for overactive bladder in diabetic patients]. Article in French. Prog Urol. 2017;27:1091–7.
38. Cui Y, Wang L, Liu L, Zeng F, Niu J, Qi L, et al. Botulinum toxin-a injections for idiopathic overactive bladder: a systematic review and meta-analysis. Urol Int. 2013;91:429–38.
39. Mohee A, Khan A, Harris N, Eardley I. Long-term outcome of the use of intravesical botulinum toxin for the treatment of overactive bladder (OAB). BJU Int. 2013;111:106–13.
40. Veeratterapillay R, Harding C, Teo L, Vasdev N, Abroaf A, Dorkin TJ, et al. Discontinuation rates and inter-injection interval for repeated intravesical botulinum toxin type a injections for detrusor overactivity. Int J Urol. 2014;21:175–8.
41. Ravindra P, Jackson BL, Parkinson RJ. Botulinum toxin type a for the treatment of non-neurogenic overactive bladder: does using onabotulinumtoxinA (Botox ®) or abobotulinumtoxinA (Dysport ®) make a difference? BJU Int. 2013;112:94–9.
42. Wang C-C, Liao C-H, Kuo H-C. Diabetes mellitus does not affect the efficacy and safety of intravesical onabotulinumtoxina injection in patients with refractory detrusor overactivity. Neurourol Urodyn. 2014;33:1235–9.
43. Osborn DJ, Kaufman MR, Mock S, Guan MJ, Dmochowski RR, Reynolds WS. Urinary retention rates after intravesical onabotulinumtoxinA injection for idiopathic overactive bladder in clinical practice and predictors of this outcome. Neurourol Urodyn. 2015;34:675–8.
44. Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn. 2015;34:224–30.
45. Peters KM, Shen L, McGuire M. Effect of sacral neuromodulation rate on overactive bladder symptoms: a randomized crossover feasibility study. Low Urin Tract Symptoms. 2013;5:129–33.
46. Davis T, Makovey I, Guralnick ML, O'Connor RC. Sacral neuromodulation outcomes for the treatment of refractory idiopathic detrusor overactivity stratified by indication: lack of anticholinergic efficacy versus intolerability. Can Urol Assoc J. 2013;7:176–8.
47. Angioli R, Montera R, Plotti F, Aloisi A, Montone E, Zullo MA. Success rates, quality of life, and feasibility of sacral nerve stimulation in elderly patients: 1-year follow-up. Int Urogynecol J. 2013;24:789–94.
48. Lai HH, Grewal S. Bacterial colonization rate of InterStim and infection outcome with staged testing. Urology. 2013;82:1255–60.
49. Daniels DH, Powell CR, Braasch MR, Kreder KJ. Sacral neuromodulation in diabetic patients: success and complications in the treatment of voiding dysfunction. Neurourol Urodyn. 2009;29:578–81.
50.•• Suh YS, Ko KJ, Kim TH, Lee HS, Sung HH, Cho WJ, et al. Potential biomarkers for diagnosis of overactive bladder patients:

urinary nerve growth factor, prostaglandin E2, and adenosine triphosphate. Int Neurourol J. 2017;21:171–7 **Urinary nerve growth factor is a potential biomarker for diagnosis of OAB.**

51.•• Park EC, Lim JS, Kim S II, et al. proteomic analysis of urothelium of rats with Detrusor overactivity induced by bladder outlet obstruction. Mol Cell Proteomics. 2018;17:948–60 **Proteins expressed in the urothelium may serve as potential biomarkers.**

52. Fırat E, Aybek Z, Akgün Ş, Küçüker K, Akça H, Aybek H. Exploring biomarkers in the overactive bladder: alterations in miRNA levels of a panel of genes in patients with OAB. Neurourol Urodyn. 2019;38:1571–8.

53. Guzman-Negron JM, Goldman HB. New devices and Technologies for the Management of overactive bladder. Curr Urol Rep. 2017;18:94.

54. Balthazar A, Cullingsworth ZE, Nandanan N, Anele U, Swavely NR, Speich JE, et al. An external compress-release protocol induces dynamic elasticity in the porcine bladder: a novel technique for the treatment of overactive bladder? Neurourol Urodyn. 2019;38:1222–8.