CHAPTER 28

UROLOGIC DISEASES AND SEXUAL DYSFUNCTION IN DIABETES

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SUMMARY

Diabetes impacts the function and structure of the lower urinary tract, including the bladder and prostate, which can lead to complications such as urinary incontinence, poor bladder emptying, sexual dysfunction, lower urinary tract symptoms (LUTS), and urinary tract infection. Although urologic complications increase with age in the general population, urologic complications are even more common in individuals with diabetes compared to those with normal glucose. It has been estimated that risk of urologic complications is increased 25% to 200% in men and about 50% to 200% in women among those with diabetes compared to those with normal glucose.

In men with diabetes, common urologic complications include LUTS and benign prostatic hyperplasia (BPH), a histological diagnosis associated with growth of the prostate gland. LUTS, the most common clinical manifestation of BPH, occur more frequently among men with diabetes compared to men with normal glucose. Similarly, men with diabetes more commonly have BPH. The interplay of LUTS, BPH, and diabetes remains unclear.

Erectile dysfunction (ED) is also common in men with diabetes, with a prevalence estimated at 23%–90%. Although less studied, type 1 diabetes appears to increase the risk of ED in a similar fashion as type 2 diabetes.

In women, sound epidemiologic evidence from several studies has linked type 1 and type 2 diabetes and urinary incontinence. Prevalence of incontinence has been estimated to be about 50%–200% more common in women with type 2 diabetes than in women with normal glucose. Data on the incidence of incontinence reflect a similar pattern. There is also evidence that women with prediabetes are at higher risk for incontinence. Less research has been conducted on women with type 1 diabetes; however, incontinence also appears to be more prevalent among women with type 1 diabetes compared with women without diabetes.

Health care providers should be alert for urologic complications among their patients with diabetes because these conditions are common and often go unrecognized and, thus, undertreated. Future research is needed to identify mechanisms and effective treatment and prevention strategies to decrease the psychosocial, medical, and economic costs of these chronic disorders in many men and women with diabetes.

INTRODUCTION

This chapter focuses on the relationships between diabetes and common or otherwise significant urologic disorders. The first sections examine associations of diabetes with lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH), and erectile dysfunction (ED) in men. Classification, pathophysiology, and data sources and limitations are discussed. The remaining sections evaluate and summarize the clinical and epidemiologic literature as described above that pertains to diabetes and urinary incontinence and sexual dysfunction in women.

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LOWER URINARY TRACT SYMPTOMS IN MEN WITH DIABETES

In men, LUTS are common, age-related complaints that are most often attributed to the histologic enlargement of the prostate, also known as BPH. BPH is the most common benign neoplasm in American men and, indeed, most often manifests clinically as the progressive development of LUTS, which are variably comprised of obstructive voiding symptoms that include urinary hesitancy, delay in initiating micturition, intermittency, involuntary interruption of voiding, weak urinary stream, straining to void, sensation of incomplete emptying, and terminal dribbling, as well as bladder storage symptoms typically represented by urinary frequency, nocturia, urgency, incontinence, and bladder pain or dysuria (1). Similar urinary symptoms also result from diabetes, and accumulating evidence indicates that diabetes may be associated with BPH.

DESCRIPTION, MEASUREMENT, CLASSIFICATION

Although several pathologies may potentially contribute to the generation of BPH-associated LUTS, BPH may induce bladder outlet obstruction by two general mechanisms: static and dynamic. The static mechanism involves hyperplastic stromal and epithelial prostate growth, which over time, compresses the prostatic urethra. The dynamic mechanism entails increased tone of prostate smooth muscle, which is mediated by the alpha-1 adrenergic receptor. Stimulation of the alpha-1 receptors induces a contraction and corresponding reduction in urethral lumen diameter. Obstruction of the bladder outlet induces two pathologic changes in the structure of the bladder that may produce LUTS. First, decreased bladder compliance causes urinary frequency and urgency. Second, decreased bladder muscle contractility—resulting from chronic tonicity as the bladder labors to overcome increased urethral pressures—may precipitate urinary hesitancy, decreased force of stream, and high residual volumes (2,3).

These relatively straightforward explanations belie the complexity of diagnosing and researching a disease that most often presents with highly subjective symptoms, has few robust objective markers, and overlaps considerably with other conditions that produce urinary symptoms. In fact, among men with diabetes, similar urinary symptoms may also result from bladder dysfunction due to denervation and poor detrusor contractility and/or detrusor overactivity resulting from neuropathy, which increases hyperactivity of the detrusor. The failure to differentiate symptoms due to BPH from those due to simple LUTS in diabetic men has contributed to the confusing evidence seen in the literature (4).

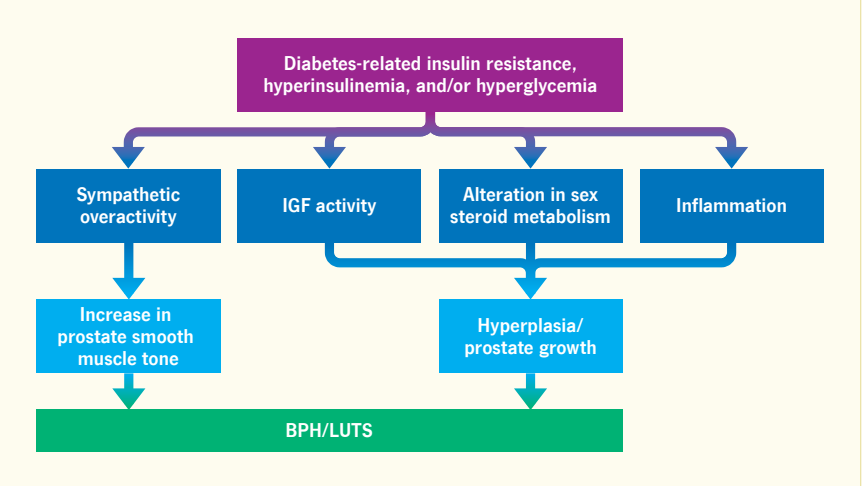
The mainstay of LUTS measurement in clinical practice, outcomes research, and clinical trials is the American Urological Association Symptom Index (AUASI), a validated symptom index developed in collaboration with the Patient Outcome Research Team for Prostate Disease (5). The AUASI is a standardized, validated, seven-item, self-reported index of LUTS in men that asks the respondent about the severity of their LUTS over the last 4 weeks on a scale of 0–5. Men are typically classified as having mild, moderate, or severe symptoms based on their summed AUASI scores, with mild symptom scores in the range of 0–7, moderate symptoms 8–19, and severe symptom scores ≥20 (5).

DATA SOURCES, LIMITATIONS

The understanding of BPH/LUTS and diabetes in men is based primarily on national and regional datasets, which include men with self-reported type 2 diabetes, as well as one randomized clinical trial on type 1 diabetes (Tables 28.1–28.3). While several international studies have examined these associations and some are discussed briefly, the majority of data presented are from U.S. regional datasets describing those with type 2 diabetes.

Given that obtaining participant report is the most common method of measuring LUTS in epidemiologic studies, several methodologic issues concerning self-reports should be considered, especially when comparing certain results across studies, such as the collection method, reference time period, and LUTS case definition. Regarding the collection method, data suggest that some participants may respond differently to LUTS items on a self-administered questionnaire versus during a telephone or face-to-face interview. Several studies have demonstrated that the values of the AUASI differ by mode of administration (6,7). Another potential source of variability across studies is the time period over which participants are asked to recall symptoms. Within a study, these variations may not

FIGURE 28.1. Hypothesized Mechanisms of Diabetes in the Pathogenesis of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms Among Men



BPH, benign prostatic hyperplasia; IGF, insulin-like growth factor; LUTS, lower urinary tract symptoms.
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TABLE 28.1. National Study of Urologic Complications of Type 2 Diabetes Among Men: Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms

STUDY, YEAR (REF.)	STUDY DESIGN; REGION	STUDY DESCRIPTION	SAMPLE SIZE	TYPE 2 DIABETES DIAGNOSIS	BPH/LUTS DIAGNOSIS
National Health and Nutrition Examination Surveys (NHANES), 1988–1994 (3)	Cross-sectional; United States	An ongoing program of nationally representative cross-sectional studies conducted by the National Center for Health Statistics to assess the health of noninstitutionalized civilians. For these years of data, adults age ≥60 years, non-Hispanic blacks, Mexican Americans, and low-income individuals are oversampled.	Variable	Self-report or fasting glucose level ≥126 mg/dL in this analysis	Self-report LUTS

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms.
SOURCE: Reference is listed within the table.

TABLE 28.2. Regional Studies of Urologic Complications of Type 2 Diabetes Among Men: Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms

STUDY, YEAR (REF.)	STUDY DESIGN; REGION(S)	STUDY DESCRIPTION	SAMPLE SIZE	TYPE 2 DIABETES DIAGNOSIS	BPH/LUTS DIAGNOSIS
Olmsted County Study of Urinary Symptoms and Health Status in Men (OCS), 1990–2002 (35)	Longitudinal; Olmsted County, Minnesota	A study of the natural history of BPH/LUTS in a community-based sample of Caucasian men; male residents age 40–79 years were randomly selected from Olmsted County, Minnesota. A validated self-administered male LUTS index (AUASI) consisting of seven questions comprising seven symptoms. Clinical exam in a subset of participants with uroflowmetry, transrectal ultrasound, and serum measurement.	2,115	Self-report	Self-report LUTS, prostate volume, peak urinary flow rates, PSA concentrations
Flint Men's Health Study (FMHS), 1996 (114)	Cross-sectional; Genesee County, Michigan	A study of the natural history of BPH/LUTS in a community-based sample of African American men; male residents age 40–79 years were randomly selected from Genesee County, Michigan. A validated self-administered male LUTS index (AUASI) consisting of seven questions comprising seven symptoms. Clinical exam in a subset of participants with uroflowmetry, transrectal ultrasound, and serum measurement.	819	Self-report, fasting serum insulin and glucose	Self-report LUTS, prostate volume, peak urinary flow rates, PSA concentrations
Boston Area Community Health Survey (BACH), 2002–2005 (115)	Cross-sectional; Boston, Massachusetts	A population-based survey, random sample of Boston-area Caucasian, African American, and Hispanic residents age 30–79 years. A validated self-administered male LUTS index (AUASI) consisting of seven questions comprising seven symptoms.	5,506	Self-report	Self-report LUTS
Baltimore Longitudinal Study of Aging (BLSA), 1993–2002 (23)	Longitudinal; Baltimore, Maryland	Community-based prospective cohort study of volunteers in Baltimore, Maryland, age ≥20 years.	422	Self-report, fasting plasma glucose	Self-report LUTS, prostate volume

AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen.
SOURCE: References are listed within the table.

TABLE 28.3. Randomized Clinical Trials With Data on Urologic Complications of Type 1 Diabetes Among Men: Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms

STUDY, YEAR (REF.)	STUDY POPULATION	RANDOMIZATION GROUPS	PRIMARY OUTCOME	DURATION	SAMPLE SIZE	TYPE 1 DIABETES DIAGNOSIS	BPH/LUTS DIAGNOSIS
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study/Urologic Complications of Diabetes (DCCT/EDIC/UroEDIC), 2010–2011 (26)	DCCT: RCT that enrolled 1,441 subjects with type 1 diabetes, age 13–39 years, in 1983–1989; trial terminated in 1993. EDIC: In 1994, enrolled 1,375 subjects from DCCT for 20-year observational study. UroEDIC: In 2002–2004 and 2010–2011, enrolled men at the 10th and 17th EDIC study visits who agreed to answer questions about LUTS.	DCCT: Intensive treatment with insulin ≥3 times per day; conventional treatment with 1–2 insulin injections per day. UroEDIC: Observational study	Diabetes complications	DCCT: mean 6.5 years EDIC: 20 years	550	Insulin dependence, as evidenced by deficient C-peptide secretion	Self-report LUTS

BPH, benign prostatic hyperplasia; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications Study; LUTS, lower urinary tract symptoms; RCT, randomized controlled trial: UroEDIC, ancillary study of urologic complications in the DCCT/EDIC cohort.
SOURCE: Reference is listed within the table.

threaten internal validity of risk factor research. However, across studies, the magnitude of odds ratios (OR) or relative risks estimated for a given risk factor could vary due to these methodologic issues. In addition, certainly comparing absolute prevalence or incidence rates of LUTS across studies with different methodologies could be challenging.

PATHOPHYSIOLOGY AND DISEASE COURSE

Diabetes may potentially influence BPH through several mechanisms (Figure 28.1) (4). First, insulin may influence BPH risk directly by increasing the transcription of genes involved in sex hormone metabolism, thus influencing androgens and estrogens, or indirectly through altered hormone metabolism as a result of obesity (3). Higher insulin is associated with lower sex hormone binding globulin, which may increase the amount of androgen/estrogen entering prostatic cells, thereby increasing the risk of BPH. Androgenic actions within the prostate where androgens bind to the androgen receptor and activate DNA synthesis and cellular proliferation may increase the risk of BPH. Finally, accumulating data suggest that inflammation may play an important role in the development of BPH and the development and progression of LUTS. While the mechanisms by which inflammation may lead to prostatic growth have not been elucidated, inflammatory mediators may contribute to prostatic epithelial and stromal cell growth both directly, through growth induction via cytokines that stimulate production of prostatic growth factors, and indirectly, through decreases in prostate cell death via down regulation of prostate cell apoptosis (8). Moreover, glucose insensitivity is a component of the metabolic syndrome. The metabolic syndrome is associated with systemic inflammation and oxidative stress; histological BPH is usually associated with inflammation, and the extent and severity of the inflammation correspond to the severity of the BPH (9,10,11).

Second, while the trophic effect of increased insulin concentrations secondary to insulin resistance might induce an enlarged prostate, high insulin levels may in turn increase sympathetic nerve activity, which probably contributes to an increase of prostate smooth muscle tone (3). BPH patients with hyperinsulinemia might have increased sympathetic nervous system activity because insulin resistance is associated with sympathetic activation, and higher sympathetic nervous activity would likely contribute to an increase of prostate smooth muscle tone. Additionally, hyperglycemia itself may play a role by increasing cystolic-free calcium in smooth muscle cells, as well as in neural tissue, thus leading to sympathetic nervous system activation. This would coincide with observations of increased LUTS severity in men with elevated postload glucose concentration, as well as with a higher percentage of glycosylated hemoglobin (A1c) compared with men with lower levels of glucose and A1c (12). Changes in insulin and glucose metabolism are associated with hypertension via stimulation of the sympathetic nervous system activity; this sympathetic activity is associated with prostate size and LUTS (13).

Third, because of its structural similarity to insulin-like growth factor (IGF), insulin can bind to the IGF receptor in prostate cells, possibly activating the receptor to induce growth and proliferation. Alternatively, as insulin levels increase, IGF-1 binding protein declines, thus increasing the bioavailability of IGF (3). Several studies have observed various components of the IGF axis to be associated with the risk of BPH and LUTS (3,14,15,16).

PREVALENCE AND INCIDENCE OF LUTS IN MEN WITH DIABETES

Diabetic cystopathy, a complication of diabetes characterized by impaired sensation of bladder fullness, increased bladder capacity, and reduced bladder contractility has been estimated to occur in 25%–45% of both male and female patients with diabetes; however, significant variability in estimates exists due to differences in case definition and measurement. The prevalence of cystopathy in men increases with the duration of diabetes (25% for 10 years, >50% for 45 years) (17). This dysfunction typically involves autonomic neuropathy leading to functional parasympathetic and possibly sympathetic denervation of the detrusor.

While much of the epidemiologic literature supports the notion that diabetes increases the occurrence of LUTS, estimates of LUTS attributable to BPH in men with diabetes are complicated by several issues. First, LUTS have multiple potential etiologies, including bladder outlet obstruction, primary bladder functional disorders (i.e., overactive bladder, interstitial cystitis), behaviors (i.e., fluid consumption), medications (i.e., diuretic use), and other medical conditions (i.e., sleep apnea), or a combination of these factors. Second, diabetes may precipitate urinary storage symptoms through neurologic mechanisms that are completely independent of any potential links with BPH, as described. As such, estimates of the prevalence of BPH/LUTS in men with diabetes are somewhat variable. In a combined analysis of two population-based cohorts, 45.9% of men with diabetes reported moderate to severe LUTS compared to 33.6% of men without diabetes (p=0.001). These estimates in both men with and without diabetes are greater than those reported by other studies, which may reflect differences in the specificity of the definitions of diabetes and older age of men in these cohorts designed to examine the natural history of BPH/LUTS. Nonetheless, the data demonstrate the potential magnitude of the frequency of BPH/LUTS in the male diabetes population (Table 28.4).

ASSOCIATIONS BETWEEN BPH/LUTS AND DIABETES

Diabetes and BPH

A preponderance of the epidemiologic literature supports the concept that diabetes is associated with objective measures of BPH, most notably prostate gland size. A series of cross-sectional studies from Sweden demonstrated that physician-diagnosed diabetes was significantly associated with increased prostate size consistent with BPH (18,19,20,21). These authors observed that in patients with LUTS, men with diabetes had a

TABLE 28.4. Type 2 Diabetes and Prevalence of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms Among Men

STUDY, YEAR (REF.)	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	BPH/LUTS PREVALENCE (%)	
			Type 2 Diabetes	No Type 2 Diabetes
Olmsted County Study of Urinary Symptoms and Health Status in Men (OCS), 1990/Flint Men's Health Study (FMHS), 1996 Combined (24)	OCS: 2,115; 105 FMHS: 369; 65	40–79	45.9	33.6
FMHS, 1996 (114)	708; 139	40–79	44.6	28.7
Boston Area Community Health Survey (BACH), 2002–2005 (115)	2,301; 247	30–79	Moderate: 6.1 Severe: 25.3	6.0

BPH, benign prostatic hyperplasia; FMHS, Flint Men's Health Study; LUTS, lower urinary tract symptoms; OCS, Olmsted County Study of Urinary Symptoms and Health Status in Men.

SOURCE: References are listed within the table.

TABLE 28.5. Type 2 Diabetes and Risk of Benign Prostatic Hyperplasia/Lower Urinary Tract Symptoms Among Men

STUDY, YEAR (REF.)	DURATION OF FOLLOW-UP	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*
Olmsted County Study of Urinary Symptoms and Health Status in Men (OCS), 1990/Flint Men's Health Study (FMHS), 1996 Combined (24)	Cross-sectional	OCS: 2,115; 105 FMHS: 369; 65	40–79	1.28 (0.88–1.85)
FMHS, 1996 (114)	Cross-sectional	708; 139	40–79	1.95 (1.49–2.57)
Baltimore Longitudinal Study of Aging (BLSA), 1993–2002 (23)	8 years	422; 45	27–84	2.80 (1.10–7.10) 2.60 (1.01–6.70)†
Boston Area Community Health Survey (BACH), 2002–2005 (115)	3 years	1,899; 284	30–79	2.87 (1.56–5.31)

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* FMHS, Flint Men's Health Study; OCS, Olmsted County Study of Urinary Symptoms and Health Status in Men.

* Comparing diabetes versus no diabetes.

† Comparing elevated fasting glucose (>110 mg/dL) versus normal fasting glucose (≤110 mg/dL).

SOURCE: References are listed within the table.

larger prostate gland than men without diabetes, 78.0 mL versus 45.0 mL (p=0.006), respectively (21). Furthermore, they observed that men with fast-growing prostate glands had a higher prevalence of type 2 diabetes (p=0.02) (18). More specifically, these and other studies also observed significant associations between increased insulin concentrations and prostate volume. In a case-control study of men with and without digital rectal exam- and transrectal ultrasound-diagnosed BPH, cases had significantly higher fasting serum insulin and homeostatic model assessment insulin resistance levels than controls (22). In the Baltimore Longitudinal Study of Aging (BLSA), men with elevated fasting glucose, defined as >110 mg/dL (>6.11 mmol/L), were threefold more likely to have an enlarged prostate (≥40 cc) as measured by magnetic resonance imaging; in men with diabetes, defined as fasting glucose levels ≥126 mg/dL (≥6.99 mmol/L) and/or history of treatment with insulin or oral hypoglycemic agents, the risk was increased twofold compared to men with normal fasting glucose ≤110 mg/dL (23). These findings suggest that BPH might be a condition associated with insulin resistance with secondary hyperinsulinemia as a possible etiologic factor for prostate enlargement.

Diabetes and LUTS

Several epidemiologic studies that have examined the association between LUTS and self-reported history of diabetes suggest that LUTS may occur more frequently among men with diabetes, with an estimated 25% to 200% increased risk of LUTS in men with diabetes. In a cross-sectional evaluation of two population-based cohorts, men with diabetes were 1.28 (95% confidence interval [CI] 0.88–1.85) times more likely to report moderate to severe LUTS compared to their nondiabetic counterparts after adjustment for age (Table 28.5) (24). Similar findings were observed in a study using National Health and Nutrition Examination Survey (NHANES) data, which demonstrated that a history of diabetes was positively associated with LUTS (OR 1.67, 95% CI 0.72–3.86) (3). In the same study, the odds of LUTS increased with increasing A1c (p=0.005). In addition, in the BLSA, men with elevated fasting glucose (>110 mg/dL) were 2.6-fold and diabetic men (fasting glucose levels ≥126 mg/dL and/or history of treatment with insulin or oral hypoglycemic agents) were 2.8-fold more likely to have LUTS than men without diabetes (Table 28.5) (23). Finally, in a German study, among 9,856 men with clinically diagnosed BPH, the presence of diabetes (13%) was associated with increased LUTS severity (OR 1.05, 95% CI 1.04–1.06), which affected voiding more than storage function (25). Patients with BPH and diabetes had a significantly higher

baseline AUASI and a significantly lower maximal urinary flow rate (Qmax) than those without diabetes (both p<0.001). The authors hypothesized that diabetes not only impairs detrusor function but also may affect bladder outlet resistance, which could occur by altering the responsiveness of smooth muscle alpha-1 adrenergic receptors, which have an important role in the regulation of bladder outlet resistance.

In the Diabetes Control and Complications Trial (DCCT) and its observational follow-up, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, randomization to intensive versus conventional treatment for type 1 diabetes in the DCCT did not reduce the risk of having moderate to severe LUTS (OR 0.84, 95% CI 0.55–1.28) (26). Several reasons may explain why this study did not demonstrate an association between glycemic control and LUTS. First, the DCCT participants had had type 1 diabetes for a significant period of time, such that the opportunity for glycemic control to influence LUTS may have passed. Second, glycemic control at the time of LUTS assessment was comparable in the treatment arms, so only effects that persisted and reflected prior glycemic exposure would have been found. Third, diabetes and glycemic control may have conflicting impacts on the prostate and bladder, such that no effect was observed. If diabetes slows down prostate growth via its impact on testosterone and growth factors, it might reduce the risk of LUTS (via obstructive mechanism) and mask beneficial effects of glycemic control on bladder dysfunction. Fourth, these men were relatively younger on average than the population of males that typically experience an increase in the frequency of LUTS. Finally, management of diabetes was very good among men assigned to conventional treatment, which might have affected the ability to detect an effect of intensive treatment on LUTS (Table 28.3).

Studies that have incorporated more objective measures of BPH, as well as LUTS, as the outcomes have reported mixed results. In the Massachusetts Male Aging Study, men with diabetes were 1.5 (95% CI 0.8–2.7) times more likely to be diagnosed with clinical BPH (defined as BPH surgery or LUTS) (27), whereas a decreased risk of BPH and increased risk of LUTS was observed among diabetic men in the California Men's Health Study (26). Finally, in a prospective cohort study examining the influence of diabetes on the progression of BPH markers, diabetic men reported a larger increase in the AUASI score than did nondiabetic men (28). However, there were no differences in change of prostate volume or prostate-specific antigen (PSA), suggesting, perhaps, that the presence of diabetes may be less directly associated with prostate growth and more closely associated with bladder dysfunction due to the diabetes itself. As there is clinical overlap between the presence of BPH and LUTS, with LUTS being the primary manifestation of BPH, the conditions can be manifestations of different pathophysiologic pathways mediated through hormonal, environmental, genetic, neuropathic, and (micro) vascular influences, particularly in the diabetic patient (29). While a substantial proportion of the existing body of literature supports an association between diabetes and LUTS, the failure to differentiate LUTS from BPH has contributed to some of the confusing evidence observed in studies including more specific measurements of BPH.

SEXUAL DYSFUNCTION IN MEN WITH DIABETES

DESCRIPTION, MEASUREMENT, CLASSIFICATION

Male sexual dysfunction can involve physiological and psychological problems with erections, ejaculation, libido, and orgasm. The majority of available data on sexual dysfunction in patients with diabetes pertains to ED, the focus of this section. The 2009 International Consultation on Sexual Dysfunctions reached the following consensus definition of ED: "ED is defined as a man's consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity. A three-month minimum duration of symptoms is accepted for establishment of the diagnosis" (30).

The mainstay of sexual dysfunction measurement in clinical practice, outcomes research, and clinical trials is the International Index of Erectile Function (IIEF) (31). The IIEF is a standardized, validated, 15-item, self-reported measure of sexual function in men that asks the respondent about their sexual function over the last 4 weeks (31). The IIEF assesses five domains of male sexual function, including desire, erectile function, orgasm, intercourse satisfaction, and overall satisfaction. Validated cutoff scores for the erectile function domain of the original IIEF (IIEF-EF) have been developed to stratify severity of ED (32). The IIEF is considered the gold standard for patient-based assessment of male sexual function by the International Society for Sexual Medicine (30). An abbreviated short form of the IIEF (Sexual Health Inventory for Men or SHIM) consisting of five questions is also available (33). Other measures of erectile health, such as penile ultrasound or penile tumescence testing, are infrequently used in clinical practice or epidemiologic research.

DATA SOURCES, LIMITATIONS

The majority of literature regarding ED in men with diabetes comes from regional datasets and national studies, with a limited amount of data from clinical trials (Tables 28.6–28.8).Some data sources did not specify type of diabetes (34,35,36,37,38,39), while others included only type 1 (40) or type 2 diabetes (41). Studies are heterogeneous in how they measure ED, with some using validated domains of instruments, such as the IIEF (36), and others asking global single item questions about erectile function (37), making study comparisons difficult.

PATHOPHYSIOLOGY AND DISEASE COURSE

The cause of diabetic ED is multifactorial (42,43). Disease pathophysiology is driven by vasculopathy, neuropathy,

TABLE 28.6. National Studies of Urologic Complications of Type 2 Diabetes Among Men: Erectile Dysfunction

STUDY, YEAR (REF.)	STUDY DESIGN	STUDY DESCRIPTION	SAMPLE SIZE	TYPE 2 DIABETES DIAGNOSIS	ED DIAGNOSIS
National Health and Nutrition Examination Surveys (NHANES), 2001–2002 (37)	Cross-sectional	The cohort (see Table 28.1) was assessed for ED using a single question during a self-paced, computer-assisted self-interview.	2,126	Self-report physician diagnosis, use of diabetes medication, 8-hour fasting glucose >126 mg/dL, or nonfasting glucose >200 mg/dL	Self-report
Health Professionals Follow-Up Study (HPFS), 1986–2000 (45)	Longitudinal	Male health care professionals in the United States followed at 2-year intervals with mailed questionnaires.	31,027	Self-report	Self-report
Male Attitudes Regarding Sexual Health Survey (MARSH), 2001–2002 (38)	Cross-sectional	Population-based, nationally representative probability survey with oversampling of minority populations by telephone.	901	Self-report	IIEF-5

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* ED, erectile dysfunction; IIEF-5, erectile function domain of the International Index of Erectile Function.

SOURCE: References are listed within the table.

TABLE 28.7. Regional Studies of Urologic Complications of Type 2 Diabetes Among Men: Erectile Dysfunction

STUDY, YEAR (REF.)	STUDY DESIGN; REGION(S)	STUDY DESCRIPTION	SAMPLE SIZE	TYPE 2 DIABETES DIAGNOSIS	ED DIAGNOSIS
Olmsted County Study of Urinary Symptoms and Health Status in Men (OCS), 1990–1996 (35)	Longitudinal; Olmsted County, Minnesota	A study of the natural history of sexual function in a community-based sample of Caucasian men; male residents age 40–79 years were randomly selected from Olmsted County, Minnesota. A validated self-administered male sexual function index consisting of 11 questions comprising five sexual function domains.	2,115	Self-report	Self-report
Boston Area Community Health Survey (BACH), 2002–2005 (34)	Cross-sectional; Boston, Massachusetts	A population-based survey; random sample of Boston-area Caucasian, African American, and Hispanic residents age 30–79 years. Sexual dysfunction was assessed with the IIEF.	5,506	Self-report	Self-report
Massachusetts Male Aging Study (MMAS), 1987–1997 (39)	Longitudinal; Boston Metropolitan area, Massachusetts	Prospective observational study that followed men, age 40–69 years with 6–9 years follow-up. Self-administered questionnaire on sexual activity. Items related to erectile function and a global subjective self-assessment were obtained.	847	Self-report	Self-report

ED, erectile dysfunction; IIEF, International Index of Erectile Function.

SOURCE: References are listed within the table.

and an altered hormonal milieu (44). Associated comorbid conditions, such as aging, hypertension, cardiac disease, obesity, and a lack of exercise, also promote ED in men with diabetes (37). Chronic illness can produce psychological and relationship difficulties that can compound sexual problems (44).

Among men with ED, those with diabetes may also have higher risk of more severe sexual dysfunction (44). In an analysis of men with ED who underwent extensive clinical phenotyping from the Exploratory Comprehensive Evaluation of Erectile Dysfunction database, compared to men without diabetes, men with diabetes reported worse ED and intercourse satisfaction at baseline, and ED had a greater impact on their emotional health (36). Data on men with longstanding type 1 diabetes from the DCCT/EDIC cohort demonstrated that diabetes promotes ED, orgasmic dysfunction, and decreased libido. ED was present in 34%, orgasmic dysfunction in 20%, and decreased libido in 55%. Of sexual dysfunction components, ED caused the most general bother and likely had the greatest impact on overall quality of life. When correlated with overall sexual satisfaction, weighted kappa statistics were highest for ED (0.84, 95% CI 0.80–0.87) and lower for orgasmic dysfunction (0.57, 95% CI 0.51–0.63) and decreased libido (0.55, 95% CI 0.48–0.63) (40). Increasing duration of diabetes is positively associated with increased risk of ED (45). In data from the Health Professionals Follow-up Study (HPFS), of men with diabetes who reported very poor ability to have and maintain an erection sufficient for intercourse, 19.7% reported duration of diabetes of 0–5 years compared to 37.1% of patients with diabetes >20 years (45). Men with diabetes had increasingly greater risk of ED with increased duration since diagnosis ($p<0.0001$).

TABLE 28.8. Randomized Clinical Trials With Data on Urologic Complications of Type 1 or Type 2 Diabetes Among Men: Erectile Dysfunction

STUDY, YEAR (REF.)	STUDY POPULATION	RANDOMIZATION GROUPS	PRIMARY OUTCOME	DURATION	SAMPLE SIZE	DIABETES DIAGNOSIS	ED DIAGNOSIS
Action for Health in Diabetes (Look AHEAD), 2001–2002 (41,116)	Overweight and obese men, age 45–75 years, with type 2 diabetes	Four-year intensive weight loss program; diabetes support and education control group.	Cardiovascular disease morbidity and mortality	Approx. 13 years (planned follow-up to 2014)	306	Self-reported type 2 diabetes with verification	Self-report (IIEF)
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study/Urologic Complications of Diabetes (DCCT/ EDIC/UroEDIC), DCCT 1983–1993, EDIC 1994–2014, UroEDIC 2003 (46,40)	DCCT: RCT that enrolled 761 men with type 1 diabetes, age 13–39 years. EDIC: In 1994, enrolled 720 subjects from DCCT for 20-year observational study. UroEDIC: ancillary study that examined ED.	DCCT: Intensive treatment with insulin ≥3 times per day; conventional treatment with 1–2 insulin injections per day. UroEDIC: Observational study	Diabetes complications	DCCT: mean 6.5 years EDIC: 20 years	571	Insulin dependence, as evidenced by deficient C-peptide secretion	Self-report (IIEF)
Vardenafil Trial in Men with Diabetes, NR (48)	Men age >18 years, in a stable heterosexual relationship, with type 1 or type 2 diabetes	Placebo, 10 mg Vardenafil, 20 mg Vardenafil, as needed for 12 weeks	IIEF, rates of vaginal penetration and successful intercourse, global assessment question about erection improvement	12 weeks	452	Self-reported	IIEF, rates of vaginal penetration and successful intercourse, global assessment question about erection improvement
Sildenafil Trial in Men with Diabetes, 1996 (49)	Men age ≥18 years, in a stable heterosexual relationship, with type 1 diabetes for ≥2 years or type 2 diabetes ≥5 years	Sildenafil with flexible dosing (25 mg, 50 mg, 100 mg) vs. placebo	Self-reported ability to achieve and maintain an erection for sexual intercourse	12 weeks	268	Self-reported type 1 or type 2 diabetes with verification	Self-report (IIEF)

DCCT, Diabetes Control and Complications Trial; ED, erectile dysfunction; EDIC, Epidemiology of Diabetes Interventions and Complications Study; IIEF, International Index of Erectile Function; NR, not reported; RCT, randomized controlled trial; UroEDIC, ancillary study of urologic complications of the DCCT/EDIC cohort.

SOURCE: References are listed within the table.

PREVALENCE OF SEXUAL DYSFUNCTION IN DIABETES

ED is prevalent among men with diabetes, with estimates ranging from 23% to 61.8% (Table 28.9) (35,45,46). In the HPFS cohort of 31,027 men, the prevalence of ED among men with diabetes (45.8%) was almost double that of men without diabetes (24.1%) (45). In the HPFS cohort, men with type 1 diabetes more often reported having poor or very poor erections (61.8%) compared to men with type 2 diabetes (46.2%). Only 6% of men with type 1 diabetes reported very good erections compared with 15.2% of men with type 2 diabetes. A similar increased prevalence of ED in men with diabetes was found in the Olmsted County Study (35). Of 1,562 men in the cohort, 53 had diabetes. The prevalence of ED in men with diabetes was 50% and only 12.5% in men without diabetes. Among all men, ED prevalence increased with age, and diabetes had a larger differential effect in younger men. In men age 40–49 years, 22.2% with diabetes reported ED compared to 2.4% without diabetes (OR 11.8, 95% CI 2.3–61.3); among men age ≥70 years, 77.8% with diabetes reported ED, while 56% without diabetes reported ED (OR 2.7, 95% CI 0.5–13.9) (35). Of men with type 1 diabetes in the prospective DCCT/EDIC, 23% reported ED (46).

INCIDENCE OF SEXUAL DYSFUNCTION IN DIABETES

Scant research exists investigating the incidence of ED among men with diabetes (Table 28.10). Two longitudinal studies have produced incidence estimates for American men with diabetes. The Massachusetts Male Aging Study reported an ED incidence of 51 cases per 1,000 person-years among men age 40–69 years with diabetes (95% CI 31.7–81.2 per 1,000 person-years) (39), approximately double the incidence rate of ED among men age 40–69 years without diabetes, 24.8 cases per 1,000 person-years (95% CI 21.4–28.7 per 1,000 person-years). In an earlier study, 78 (28%) of 275 potent men with diabetes developed ED over a 5-year period (47).

ASSOCIATION BETWEEN SEXUAL DYSFUNCTION AND DIABETES

Compared to men without diabetes, men with diabetes have increased odds of reporting ED in multiple studies from the United States (Table 28.11) (34,35,37,38). In adjusted models comparing men with and without diabetes, having diabetes increased the odds of reporting ED by 2.1–4.2 times (34,35,37,38). In the Male Attitudes Regarding Sexual Health survey, a total of 2,173 men participated in a nationally representative probability survey of the prevalence and correlates of ED (38). In an adjusted model, men with diabetes had a 2.1 (95% CI 1.2–3.7) times increased odds of reporting ED compared with men without diabetes. In this cohort, having diabetes increased the odds of reporting ED more than other comorbidities, including hypercholesterolemia (OR 0.9, 95% CI 0.6–1.5), hypertension (OR 1.6, 95% CI 1.0–2.4), or ischemic heart disease (OR 1.5, 95% CI 0.8–2.8). An analysis of the NHANES based on 2,126 male participants in 2001–2002, showed that men with diabetes had nearly three times increased odds (OR 2.91, 95% CI 1.47–5.73) of reporting ED compared to men without diabetes (37). Similarly, in results from the Boston Area Community Health (BACH) survey, having diabetes increased the odds of reporting ED 2.96 (95% CI 1.8–4.86) times (34). BACH included 2,301 men age 30–79 years, of whom 296 had diabetes. In a multivariate analysis of the Olmsted County Survey, men with diabetes had a 4.2 (95% CI 2.2–8.0) times increased odds of reporting ED compared to men without diabetes (35).

Data from clinical trials has informed treatment recommendations for men with diabetes and ED (Table 28.8) (41,46,48,49). Two were ancillary studies from larger randomized trials looking at ED as a secondary outcome (41,46), while the others were placebo controlled randomized trials investigating the utility of phosphodiesterase inhibitors in men

TABLE 28.9. Diabetes and Prevalence of Erectile Dysfunction Among Men

STUDY, YEAR (REF.)	SAMPLE SIZE BY TYPE OF DIABETES	AGE (YEARS)	ED PREVALENCE (%)	
			Diabetes	No Diabetes
Health Professionals Follow-up Study (HPFS), 1986–2000 (45)	Total population: 31,027 Type 1 diabetes: 51 Type 2 diabetes: 2,057	53–90	All diabetes: 45.8 Type 1: 61.8 Type 2: 45.2	24.1
Olmsted County Study of Urinary Symptoms and Health Status in Men (OCS), 1990–1996 (35)	Total population: 1,562 Diabetes, unknown type: 53	40–79	All diabetes: 50	12.5
Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study/Urologic Complications of Diabetes Ancillary Study of the DCCT/EDIC (DCCT/EDIC/UroEDIC), DCCT 1983–1993, EDIC 1994–2014, UroEDIC 2003 (46)	Type 1 diabetes: 571	44.6±6.6*	Type 1: 23	NA

ED, erectile dysfunction; NA, not applicable.
* Mean±standard deviation
SOURCE: References are listed within the table.

TABLE 28.10. Type 2 Diabetes and Incidence of Erectile Dysfunction Among Men

STUDY, YEAR (REF.)	DURATION OF FOLLOW-UP	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	INCIDENCE PER 1,000 PERSON-YEARS (95% CONFIDENCE INTERVAL)
Massachusetts Male Aging Study (MMAS), 1987–1997 (39)	8.8 years	847; 17	40–69	Diabetes: 50.7 (31.7–81.2) No diabetes: 24.8 (21.4–28.7)

SOURCE: Reference is listed within the table.

TABLE 28.11. Type 2 Diabetes and Risk of Erectile Dysfunction Among Men

STUDY, YEAR (REF.)	STUDY DESIGN	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*
Male Attitudes Regarding Sexual Health Survey (MARSH), 2001–2002 (38)	Cross-sectional	2,173; NR	40–≥70	2.1 (1.2–3.7)
National Health and Nutrition Examination Surveys (NHANES), 2001–2002 (37)	Cross-sectional	2,126; NR	20–≥70	2.91 (1.47–5.73)
Olmsted County Survey of Urinary Symptoms and Health Status in Men (OCS), 1990–1996 (35)	Cross-sectional	1,562; 53	40–79	4.2 (2.2–8.0)
Boston Area Community Health Survey (BACH), 2002–2005 (34)	Cross-sectional	2,301; 296	30–79	2.96 (1.8–4.9)

NR, not reported.
* Comparing diabetes versus no diabetes.
SOURCE: References are listed within the table.

with diabetes (48,49). In an ancillary study of the Action for Health in Diabetes (Look AHEAD) cohort that examined ED as an outcome, overweight men with type 2 diabetes were randomly assigned to either a diabetes support and education group (control) or to an intensive lifestyle intervention group (intervention) that sought to reduce weight by 7% and increase physical activity (41). The weight loss intervention was mildly helpful in maintaining erectile function but did not appear to significantly improve it. From baseline to one year, 8% of men who underwent the intervention reported worsening ED, 70% stayed the same, 22% improved. In contrast, in the control group, 20% reported worsening, 57% stayed the same, 23% improved (p=0.006). UroEDIC, an ancillary study assessing the urologic complications in the DCCT/EDIC cohort, examined erectile function in men with type 1 diabetes who had been assigned to conventional versus intensive glycemic therapy in the DCCT. Overall, the risk of ED was directly associated with mean A1c levels during the trial. The authors contend that the results support early implementation of intensive insulin therapy in young men with type 1 diabetes. In addition to weight loss and glycemic control, primary treatment for ED in men with diabetes may include medical management with erectile aids. Both sildenafil and vardenafil, phosphodiesterase inhibitors used to treat erectile dysfunction, have been shown in randomized trials to be efficacious and well-tolerated for the treatment of ED in men with diabetes (48,49).

LOWER URINARY TRACT SYMPTOMS IN WOMEN WITH DIABETES

In women, LUTS, which include urinary incontinence (UI), bladder storage symptoms, sensory symptoms, and voiding and postmicturition symptoms, are increasingly recognized in those with diabetes (50). Bladder storage symptoms in women include increased daytime urinary frequency, nocturia, urgency, and overactive bladder (OAB) syndrome (i.e., urinary urgency, often accompanied by nocturia and frequency, with or without urgency UI leakage, in the absence of urinary tract infection or other obvious pathology) (50). Sensory symptoms occur during bladder filling and include increased, reduced, or absent bladder sensation (50). Voiding and postmicturition smptoms include hesitancy, slow stream, intermittency, straining to void, feeling of incomplete bladder emptying, postmicturition leakage, dysuria, and urinary retention (50). Overall, UI has received by far the greatest amount of attention in the epidemiologic literature on the urologic complications of diabetes among women in the United States and is the focus of this section.

DESCRIPTION, MEASUREMENT, CLASSIFICATION

UI is defined as involuntary loss of urine (50). Several types of UI, which are thought to have different etiologies, are generally distinguished in epidemiologic research: stress UI, defined as involuntary loss of urine with physical exertion, sneezing, or coughing; urgency UI, defined as involuntary loss of urine associated with a strong, sudden desire to void; and mixed UI, defined as involuntary loss of urine associated with both physical exertion, sneezing or coughing, and a strong, sudden desire to void (50). Generally, among younger women, stress UI is the most common type of incontinence. However, with increasing age, the ratio of stress to urgency UI tends to decrease, and mixed UI becomes the dominant UI type (51).

Clinical diagnosis of UI, and more broadly LUTS, may be based on a variety of factors, including the woman's complaint, observation of the symptom on examination, records of the symptom on bladder diaries completed by the woman, perineal pad weighing (for UI), and urodynamic testing (50). In large epidemiologic studies, however, clinical testing to diagnose LUTS is generally not practical. Yet, self-reported LUTS have been found to have moderate to high validity compared with clinical diagnoses (52,53). In addition, self-reported symptoms may have benefits over clinical examination; for example, UI symptoms can vary over time and may simply be absent on any given day despite their occurence on other days. Validation studies indicate that specific UI types are not reported as accurately as UI overall, although specificity generally is high (e.g., 88%–96% specificity), with lower sensitivity for self-reported stress and urgency UI (e.g., 56%–66% sensitivity) compared with clinical diagnosis (54).

Methodologic issues associated with self-reported LUTS are described in the section above on LUTS in men with diabetes. In addition to the previously described issues (i.e., varying collection method and reference time period), it is important to note that differences in the wording of questions about UI and UI case definitions (e.g., UI episodes occurring at least once per month versus at least once per week) may contribute to variable findings among studies. Again, while these sources of variation may not threaten internal validity of risk factor research within a study, they should be considered when comparing association measures or absolute prevalence or incidence rates of LUTS across studies.

DATA SOURCES, LIMITATIONS

The understanding of LUTS in women with diabetes is based on national and regional datasets, as well as randomized clinical trials (Tables 28.12–28.14). Nonetheless, the majority of data are from more regional datasets, and limited information is available on broader-based populations, including minorities. Thus, the existing data may or may not apply to specific groups, such as African Americans, Hispanics, or Asian Americans. In addition, given the substantial resources required to conduct prospective studies versus cross-sectional studies, few studies have collected prospective data on LUTS among women with or without diabetes; thus, relatively little is known regarding the incidence and natural history of LUTS.

Another limitation of the U.S. literature on diabetes and LUTS in women is the minority of studies that have reported

on LUTS other than UI. Notable exceptions are the BACH survey and the Reproductive Risks of Incontinence Study at Kaiser (RRISK), which have provided information on a broad variety of LUTS in U.S. women. In general, findings regarding the relation of type 2 diabetes to broader LUTS are somewhat weaker than those for UI alone, perhaps because LUTS represent a broader spectrum of conditions and etiologies. For example, an analysis using BACH survey data examined the relation between type 2 diabetes and LUTS overall, defined as an AUASI score ≥8, as well as eight specific LUTS (UI, painful bladder syndrome, frequency, urgency, nocturia, OAB, OAB with urgency incontinence, and OAB without urgency incontinence) among 3,205 women (55). After adjusting for potential confounding factors, the odds of prevalent nocturia were significantly higher among women with than without type 2 diabetes (p=0.002); but, type 2 diabetes was not statistically significantly associated with LUTS overall or any of the other individual LUTS, although marginally significant associations with greater prevalence of UI and frequency were observed (55). In addition, 427 women with type 2 diabetes in RRISK reported symptoms of stress and urgency UI, daytime urinary frequency, nocturia, and obstructive voiding (defined as reporting incomplete emptying, intermittent stream, weak stream, or abdominal straining about half the time or more) (56). Prevalence percentages were 20% for daytime urinary frequency, 18% for nocturia, and 21% for obstructive voiding. The unadjusted prevalence of any urinary symptom (defined as UI, daytime urinary frequency, nocturia, or obstructive voiding) was slightly higher among women with type 2 diabetes compared with women in RRISK without diabetes (56% vs. 49%, p<0.001) (56). Additional studies assessing the broad spectrum of LUTS in women with diabetes are needed.

Another possible limitation in the UI literature, which is the focus of this section, is the lack of attention to bother; several epidemiologic studies have inquired about bother associated with symptoms (57,58,59,60), but most have

TABLE 28.12. National Studies of Urologic Complications of Type 2 Diabetes Among Women

STUDY, YEAR (REF.)	STUDY DESIGN	STUDY DESCRIPTION	NUMBER OF WOMEN	SURVEY MODE OF ADMINISTRATION	TYPE 2 DIABETES DIAGNOSIS	UI QUESTION(S)
Health and Retirement Study (HRS), 2000 (117)	Longitudinal	A longitudinal study of older Americans. Data have been collected biennially since 1992. Potential participants were selected via a national multistage area probability sample of households in the United States. Black and Hispanic women were oversampled.	10,678	Telephone or in-person interview	Self-report of physician diagnosis	During the last 12 months, have you lost any amount of urine beyond your control? On about how many days in the last month have you lost any urine?
National Health and Nutrition Examination Surveys (NHANES), 2001–2002 (57)	Cross-sectional	An ongoing program of nationally representative cross-sectional studies conducted by the National Center for Health Statistics to assess the health of noninstitutionalized civilians. For these years of data, adults age ≥60 years, non-Hispanic blacks, Mexican Americans, and low-income individuals are oversampled.	1,461	In-person interview (type 2 diabetes); self-administered questionnaire (LUTS)	Self-report of physician diagnosis or fasting glucose level ≥126 mg/dL	During the past 12 months, have you leaked or lost control of even a small amount of urine with: 1. an activity like coughing? 2. an urge or pressure to urinate and you could not get to the toilet fast enough?*
NHANES, 2001–2004 (58)	Cross-sectional	Same as above.	4,229	In-person interview	Self-report of physician diagnosis or ever use of insulin or diabetes pills	Same as above.
Nurses' Health Study (NHS), 1996–2004, NHS II, 2001–2005 (71,79,82,118)	Longitudinal	The NHS, initiated in 1976 in women age 30–55 years, and the NHS II, initiated in 1989 in women age 25–42 years, enrolled registered nurses residing in the United States. Since enrollment, participants have reported information on health and lifestyle via biennial questionnaires. Over 95% of women in the cohorts are white.	NHS: 121,700 NHS II: 116,430	Mailed questionnaire	Self-report of physician diagnosis with verification (supplemental questionnaire requesting details on symptoms, diagnostic tests, and treatment)	During the past 12 months, how often have you leaked or lost control of your urine?†

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. LUTS, lower urinary tract symptoms; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; UI, urinary incontinence.
* Data on level of bother associated with urine leakage, effect of incontinence on quality of life, degree of worry created by urine leakage, and effect of urine leakage on day-to-day activities were also collected.
† Data on usual amount of urine leakage and urinary incontinence type were also collected.
SOURCE: References are listed within the table.

TABLE 28.13. Regional Studies of Urologic Complications of Type 2 Diabetes Among Women

STUDY, YEAR (REF.)	STUDY DESIGN; REGIONS	STUDY DESCRIPTION	NUMBER OF WOMEN	SURVEY MODE OF ADMINISTRATION	TYPE 2 DIABETES DIAGNOSIS	UI QUESTION(S)
Boston Area Community Health Survey (BACH), 2002–2005 (77,55)	Cross-sectional; Boston, Massachusetts	A population-based epidemiologic survey conducted in a random sample of Boston-area Caucasian, African American, and Hispanic residents age 30–79 years at baseline. Data on a broad range of urologic symptoms and risk factors were collected.	3,205	In-person interview	Self-report of physician diagnosis	Many people complain that they leak urine (wet themselves) or have accidents. In the last 12 months, have you leaked even a small amount of urine? American Urological Association Symptom Index*
Diabetes and Aging Study, 2005–2006 (63)	Cross-sectional; Northern California	A substudy of the Diabetes Study of Northern California (DISTANCE), which enrolled an ethnically stratified random sample of patients in the Kaiser Permanente Northern California Diabetes Registry. DISTANCE enrolled 40,735 patients (19,377 women) age 30–75 years with both type 1 and type 2 diabetes.	6,036	Computer-assisted telephone interview, web-based survey, or self-administered written questionnaire	Kaiser Permanente Northern California Diabetes Registry	Do you experience occasional accidental leakage of urine?
Diabetes Reproductive Risk factors for Incontinence Study at Kaiser (Diabetes RRISK), 1999–2008 (85,59,56)	Longitudinal; Northern California	A study of randomly selected female members of a prepaid group practice with and without diabetes. Extensive data on diabetes severity (duration, treatment, glycemic control, and complications of diabetes) were collected. Enrollment was designed to achieve a distribution of 40% white, 20% black, 20% Hispanic, and 20% Asian participants.	2,270	In-person interview	Self-report with verification (Kaiser diabetes registry or fasting blood glucose ≥126 mg/dL)	During the past 3 months, how often have you typically leaked urine, even a small amount?†
Group Health Cooperative of Puget Sound (GHC), 1998–2002 (87,83)	Cross-sectional; Several counties of Washington state	A study of postmenopausal women age 55–75 years who were members of the GHC health maintenance organization for at least 1 year. Women were originally recruited for a study of urinary tract infection, which might have led to a higher prevalence of urinary incontinence in women with and without diabetes compared with other studies. Approximately 88% of participants are white.	1,017	Interview	Self-report of physician diagnosis, inclusion in GHC diabetes registry, or fasting glucose >125 mg/dL	Have you had accidental leakage of your urine during the past year?‡
Health, Aging, and Body Composition (Health ABC) Study, 1997–1998 (81)	Cross-sectional; Pittsburgh, Pennsylvania; Memphis, Tennessee	A study of well-functioning men and women age 70–79 years established to investigate relationships among disease, body composition, social and behavioral factors, physical function, disability, and mortality. Enrollment was limited to adults with no difficulty walking one-quarter mile, climbing 10 steps, or performing activities of daily living.	1,584	Questionnaire	Self-report and abnormal glucose testing	Many people complain that they leak urine unintentionally. In the past 12 months, have you leaked even a small amount of urine? In the past 12 months, how often have you leaked urine?§
Study of Women's Health Across the Nation (SWAN), 1995–2002 (76,86,69,119)	Longitudinal; Boston, Massachusetts; Chicago, Illinois; Detroit area, Michigan; Los Angeles, California; Newark, New Jersey; Pittsburgh, Pennsylvania; Oakland, California	A study of the natural history of the menopausal transition. Women were identified using random sampling from census lists, commercial electric utility household lists, Kaiser Permanente membership lists, or random digit dialing. Eligible women were age 42–52 years, pre- or early peri-menopausal, and not currently using exogenous hormones. At baseline, 47% of participants were white, 28% black, 9% Hispanic, 8% Chinese American, and 9% Japanese American.	3,302	Self-administered questionnaire (urinary incontinence); telephone or in-person interview (diabetes)	Self-report of physician diagnosis or serum glucose >125 mg/dL	In the past year, have you ever leaked even a small amount of urine involuntarily?‖

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. GHC, Group Health Cooperative of Puget Sound; UI, urinary incontinence.

* Data on urinary incontinence type were also collected.

† Data on urinary incontinence type, incontinence care seeking, beliefs about incontinence, and bother associated with incontinence were also collected.

‡ Data on usual amount of urine loss and urinary incontinence type were also collected.

§ Data on urinary incontinence type were also collected.

‖ Data on urinary incontinence type and level of bother associated with urine leakage were also collected.

SOURCE: References are listed within the table.

TABLE 28.14. Randomized Clinical Trials With Data on Urologic Complications of Type 1 or Type 2 Diabetes Among Women

STUDY, YEAR (REF.)	STUDY POPULATION	RANDOMIZATION GROUPS	PRIMARY OUTCOME	DURATION	NUMBER OF WOMEN	TYPE 1 OR TYPE 2 DIABETES DIAGNOSIS	UI QUESTION(S)
Action for Health in Diabetes (Look AHEAD), 2001–2005 (70,91)	Overweight and obese women, age 45–74 years, with type 2 diabetes.	Four-year intensive weight loss program; diabetes support and education control group	Cardiovascular disease morbidity and mortality	Approx. 13 years (planned follow-up to 2014)	2,994	Self-reported type 2 diabetes with verification*	In the past 12 months, have you leaked even a small amount of urine?†
Diabetes Prevention Program (DPP), 1996–2002 (89)	Men and women, age ≥25 years, at risk for diabetes (BMI ≥24 kg/m², fasting plasma glucose level 95–125 mg/dL, and 2-hour postchallenge glucose level 140–199 mg/dL).	Low-fat diet and moderate-intensity physical activity for at least 150 min/week to lose and maintain ≥7% of initial body weight; 850 mg metformin twice daily; placebo twice daily	Type 2 diabetes	2.9 years	1,957	Fasting plasma glucose ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL after a 75g oral glucose load	In the past 12 months, how often have you leaked even a small amount of urine?‡
Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications Study/Urologic Complications of Diabetes (DCCT/ EDIC/UroEDIC), 2002–2004 (88,60)	DCCT: RCT that enrolled 680 women with type 1 diabetes, age 13–39 years, in 1983–1989; trial terminated in 1993. EDIC: In 1994, enrolled 655 women from DCCT for 20-year observational study. UroEDIC: Enrolled 550 women at the 10th EDIC study visit who agreed to answer questions about urinary incontinence.	DCCT: Intensive treatment with insulin ≥3 times per day; conventional treatment with 1–2 insulin injections per day. UroEDIC: Observational study	Diabetes complications	DCCT: mean 6.5 years EDIC: 20 years	550	Insulin dependence, as evidenced by deficient C-peptide secretion	During the past 12 months how often have you leaked even a small amount of urine?§
Heart and Estrogen/ progestin Replacement Study (HERS), 1993–1994 (80)	Postmenopausal women age ≤80 years with coronary heart disease and a uterus. Women who had used sex hormones within the prior 3 months or were believed to be at risk for adverse effects of hormone therapy were excluded.	Oral daily conjugated estrogens (0.625 mg) and medroxy-progesterone acetate (2.5 mg); placebo	Coronary disease events	4 years	2,763	Self-report	During the prior week, how many times, on average, have you: 1. had to go to the bathroom to urinate during the day? 2. had to get up at night to go to the bathroom to urinate? 3. unintentionally leaked some urine with coughing, sneezing, straining, laughing, or lifting? 4. unintentionally leaked some urine before you could get to the bathroom?

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions.* BMI, body mass index; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications Study; RCT, randomized controlled trial; UI, urinary incontinence; UroEDIC, ancillary study of urologic complications of the DCCT/EDIC cohort.

* Specific methods of verification included medical records, current treatment, personal health care provider, fasting glucose ≥126 mg/dL, symptoms of hyperglycemia with casual plasma glucose ≥200 mg/dL, or 2-hour plasma glucose ≥200 mg/dL after a 75g oral glucose load on at least two occasions.

† Women with weekly incontinence in the last year were also asked to recall the type and number of incontinence episodes in the past 7 days.

‡ Women with weekly incontinence in the last year were also asked questions about urinary incontinence type.

§ Type of incontinence during the past 7 days was assessed among women with weekly incontinence. Other assessments included amount of urine lost per incontinence episode, level of bother of incontinence, and interference of incontinence with activities.

SOURCE: References are listed within the table.

not. Although the 2010 International Urogynecological Association/ International Continence Society definition of the symptom of UI does not require subjective assessment that the incontinence is a bother or problem (50), lack of information on bothersome UI could be considered a limitation, as it is a significant predictor of care seeking and quality-of-life impact (61,62). However, it is important to note that, in addition to severity of UI symptoms, perception of bother may be influenced by factors such as level of education, overall health status, presence of comorbid conditions, and belief that UI is a natural part of aging (61,62). Thus, the value of assessing bother related to LUTS likely depends on the specific study question of interest. For example, measurement of bother may be less useful for epidemiologic studies exploring etiologic hypotheses but may be advantageous when approaching hypotheses related to quality-of-life outcomes or care seeking (63).

PATHOPHYSIOLOGY AND DISEASE COURSE

The precise mechanisms underlying urologic complications of diabetes are not yet understood. However, several mechanisms that might explain a link between diabetes and LUTS have been hypothesized, mainly based on data from animal studies. These mechanisms include diabetic neuropathy and microvascular damage, leading to detrusor muscle and urothelium dysfunction (29,64). For example, over the long term, microvascular and neuronal damage resulting from diabetes may compromise innervation of the lower urinary tract and detrusor muscle, leading to the hallmark features of diabetic cystopathy: decreased bladder sensation, decreased detrusor muscle function, increased bladder volume, and overdistention (65). Indeed, evidence of impaired detrusor muscle function was observed among 427 women age 40–80 years with type 2 diabetes in the RRISK (56). Specifically, among these women, postvoid residual volume, an indicator of bladder emptying adequacy, ranged from 0 to 824 mL, with a mean of 42.0 mL (standard deviation 77.5 mL); 26% of the women had a postvoid residual volume of ≥50 mL, a level considered above normal (56,66). In contrast, among 96 mainly healthy women without significant LUTS, age ≥45 years, postvoid residual volumes were lower, ranging from 0 to 145 mL, with a mean of 24 mL (standard deviation 28 mL); 15% had a postvoid residual volume ≥50 mL (67). Although multiple mechanisms can explain increased postvoid residual volume (e.g., bladder outlet obstruction), these data suggest that impaired detrusor muscle contractility related to diabetic cystopathy is one potential factor.

In addition, several hypotheses have been proposed to explain increased involuntary detrusor muscle contractions and OAB in women with diabetes. For example, experimental studies of rat bladder strips suggest diabetes increases responsiveness of bladder tissue to electrical field stimulation (64), possibly by promoting changes in membrane lipid composition, increasing neurotransmitter release, increasing calcium-channel activity, or enhancing calcium sensitivity (64). OAB may also occur as a consequence of multiple cerebral infarctions due to diabetic cerebral vasculopathy (68). Finally, the urothelium, a key sensory organ necessary for proper bladder function, has been shown in animal studies to increase in thickness with longer diabetes duration (29). Urothelial release of prostaglandins appears to increase in proportion to the increase in urothelium thickness, resulting in increased sensitivity of the bladder smooth muscle, a change which theoretically could promote detrusor overactivity and OAB symptoms (64,65).

Data indicating higher prevalence of UI even in women at high risk for diabetes (i.e., impaired fasting glucose), and thus without apparent complications of diabetes, suggest that other unknown mechanisms underlie the development of UI. In addition, although diabetes has been associated with increased UI prevalence and incidence, it should be noted that obesity is a strong risk factor for both type 2 diabetes and UI (29); many epidemiologic study findings described in this section were adjusted for body mass index (BMI). Thus, the increase in UI with diabetes cannot be solely attributable to independent effects of BMI.

PREVALENCE OF UI IN WOMEN WITH TYPE 2 DIABETES

Overall UI

Estimates of the prevalence of weekly UI, a severity level generally considered clinically significant, range from 24% to 49% in women with type 2 diabetes (Table 28.15). In general, after accounting for potential confounding variables, including BMI and/or waist circumference, odds ratios for weekly UI comparing women with diabetes to those without diabetes indicate modest increased odds (i.e., 20%–50% higher) in those with diabetes, although in the Study of Women's Health Across the Nation (SWAN), the odds of prevalent weekly UI was 3.1 times higher in women with diabetes (Table 28.16) (69). In addition, an analysis of data from the NHANES 2001–2002 indicated that the prevalence of UI is similar in women with diabetes (35%) and women with impaired fasting glucose (33%), defined as fasting plasma glucose between 100 and 125 mg/dL (5.55–6.94 mmol/L) (Table 28.15) (57), and significantly higher than the prevalence of UI in women without diabetes (17%, $p<0.001$), even after adjusting for BMI, suggesting that urologic complications should be evaluated in prediabetes as well.

Less data are available on racial disparities in UI among women with diabetes. However, data from two studies indicate that weekly UI is more common in white women with type 2 diabetes than in African American or Asian American women with type 2 diabetes (Table 28.17) (70,71). A higher prevalence of UI in white women compared with African American or Asian American women has also been observed in studies of women without diabetes (72,73,74,75,76,77,78,79).

UI Type

Few studies have reported the prevalence of specific UI types among women with diabetes. Yet, existing data indicate that urgency UI is particularly increased

TABLE 28.15. Type 2 Diabetes and Prevalence of Weekly Urinary Incontinence Among Women

STUDY, YEAR (REF.)	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	UI PREVALENCE (%)	
			Type 2 Diabetes	No Type 2 Diabetes
Group Health Cooperative of Puget Sound (GHC), 1998–2000 (87)	1,017; 218	55–75	49	42
Action for Health in Diabetes (Look AHEAD), 2001–2004 (70)	2,994; 2,994	45–76	27.1	NA
National Health and Nutrition Examination Surveys (NHANES), 2001–2002 (57)	1,461; 246 (+164 IFG)	≥20	35.4 (IFG: 33.4)	16.8
Nurses' Health Study (NHS), 1996–2000 (82)	81,845; 4,277	50–75	24.4	17.1
Reproductive Risk factors for Incontinence Study at Kaiser (Diabetes RRISK), 1999–2003 (59)	2,270; 486	40–69	35.4	24.7

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. IFG, impaired fasting glucose, 100–125 mg/dL; NA, not applicable; UI, urinary incontinence.

SOURCE: References are listed within the table.

TABLE 28.16. Type 2 Diabetes and Odds of Prevalent Weekly Urinary Incontinence Among Women

STUDY, YEAR (REF.)	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*
Boston Area Community Health Survey (BACH), 2002–2005 (77)	3,205; NR	30–79	1.17 (0.73–1.88)
Group Health Cooperative of Puget Sound (GHC), 1998–2000 (87)	1,017; 218	55–75	1.5 (0.8–2.5)
Nurses' Health Study (NHS), 1996–2000 (82)	81,845; 4,277	50–75	1.28 (1.18–1.39)
Nurses' Health Study II (NHS II), 2001 (79)	83,355; 5,539	37–54	1.18 (1.10–1.26)
Study of Women's Health Across the Nation (SWAN), 1995–1997 (69)	2,702; 126	42–52	3.10 (1.43–6.74)

NR, not reported.

* Comparing diabetes versus no diabetes. All odds ratios were adjusted for body mass index and/or waist circumference in addition to other variables.

SOURCE: References are listed within the table.

TABLE 28.17. Type 2 Diabetes and Prevalence of Weekly Urinary Incontinence by Race/Ethnicity Among Women

STUDY, YEAR (REF.)	AGE (YEARS)	URINARY INCONTINENCE PREVALENCE (%)					
		Non-Hispanic White	White	African American	Hispanic	Asian American	Native American/ Alaska Native
Action for Health in Diabetes (Look AHEAD), 2001–2004 (70)	45–74	31.5	NR	17.8	21.9	12.1	30.8
Nurses' Health Study (NHS), 2000–2004, NHS II, 2001–2005 (71)	37–79	NR	30 (95% CI 29–31)	21 (95% CI 16–26)	NR	17 (95% CI 10–24)	NR

CI, confidence interval; NR, not reported.

SOURCE: References are listed within the table.

TABLE 28.18. Type 2 Diabetes and Urinary Incontinence Prevalence by Incontinence Type Among Women

STUDY, YEAR (REF.)	URINARY INCONTINENCE PREVALENCE (%)							
	STRESS			URGENCY			MIXED	
	Type 2 Diabetes	IFG	No Type 2 Diabetes	Type 2 Diabetes	IFG	No Type 2 Diabetes	Type 2 Diabetes	No Type 2 Diabetes
Action for Health in Diabetes (Look AHEAD), 2001–2004*† (70)	13.2	NR	NR	10.0	NR	NR	2.1	NR
National Health and Nutrition Examination Surveys (NHANES), 2001–2002* (57)	30.2	31.2	14.4	26.4	24.6	7.7	NR	NR
NHANES, 2001–2004‡ (58)	19.8	NR	25.0	10.5	NR	7.7	29.9	16.0

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. IFG, impaired fasting glucose, 100–125 mg/dL; NHANES, National Health and Nutrition Examination Survey; NR, not reported.

* Urinary incontinence was defined as weekly leakage.

† All women in Look AHEAD had type 2 diabetes.

‡ Urinary incontinence was defined as any leakage.

SOURCE: References are listed within the table.

among women with diabetes compared to women without diabetes (Table 28.18). For example, in the NHANES 2001–2002 (57), among women with diabetes or impaired fasting glucose, the prevalence of stress UI was similar to the prevalence of urgency UI (30% vs. 26% for diabetes, 31% vs. 25% for impaired fasting glucose); in contrast, among women with normal glucose, stress UI was 1.8 times more common than urgency UI (14% vs. 8%), suggesting disproportionately more urgency UI associated with diabetes. Although data are limited, several multivariable-adjusted analyses have confirmed a higher prevalence of urgency UI in women with diabetes compared to those without diabetes (Table 28.19) (69,80,81).

INCIDENCE OF UI IN WOMEN WITH TYPE 2 DIABETES

Information concerning the incidence of UI among women with diabetes in the United States is sparse. Similar to data on prevalent UI, existing data suggest that UI incidence is higher among women with diabetes versus those with normal glucose levels. For example, in the Nurses' Health Study (NHS), which examined development of weekly UI over 4 years, the incidence was 11% among women with type 2 diabetes and was almost 40% lower, at 7%, among women without diabetes (82). Multivariable-adjusted relative risks for incident UI comparing diabetes to no diabetes are comparable to those for prevalent UI, with 20%–50% higher rates of UI development in women with diabetes (Table 28.20). Although even fewer data on diabetes and incident UI type are available, study findings also suggest that women with diabetes develop urgency UI disproportionately (Table 28.20).

REMISSION AND IMPROVEMENT OF UI IN WOMEN WITH TYPE 2 DIABETES

Although it is known that UI can remit and relapse (83,84), little is known regarding changes in UI frequency among women with type 2 diabetes. Initial data suggest that UI improvement and remission may be less common in women with type 2 diabetes compared with those without diabetes (Table 28.21). For example, among 390 women with weekly UI in RRISK, the odds of UI improvement were 54% lower in women who developed type 2 diabetes during the 5-year follow-up period compared with those who did not develop diabetes (unadjusted OR 0.46, 95% CI 0.15–1.40) (85). UI improvement or remission was also less common in women with type 2 diabetes in both the SWAN and Group Health Cooperative of Puget Sound (GHC) (83,86), although differences between women with and without diabetes were smaller than in the RRISK study (Table 28.21).

CHARACTERISTICS OF TYPE 2 DIABETES AND ODDS OF UI IN WOMEN

Studies have considered the odds of UI in relation to specific characteristics of type 2 diabetes, such as duration of diabetes, glycemic control, type of treatment, and presence of complications of diabetes (Table 28.22). For example, those with long duration of diabetes have been examined; existing data do not indicate a clear increase in UI prevalence in women with longer duration of diabetes. In the NHS and NHS II, the odds of prevalent UI were modestly increased in women with type 2 diabetes for >10 years versus <5 years (adjusted OR 1.17, 95% CI 1.03–1.33) (71). In contrast, in the GHC, the odds of prevalent UI were similar in women with type 2 diabetes for <10 years (adjusted OR 1.4, 95% CI 0.8–2.6) and those with type 2 diabetes for ≥10 years (adjusted OR 1.6, 95% CI 0.7–3.4), compared with women without diabetes (87).

TABLE 28.19. Type 2 Diabetes and Odds of Prevalent Urinary Incontinence by Incontinence Type Among Women

STUDY, YEAR (REF.)	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*		
	Stress	Urgency	Mixed
Heart and Estrogen/progestin Replacement Study (HERS), 1993–1994 (80)	0.82 (0.58–1.14)	1.49 (1.11–2.00)	1.32 (1.04–1.67)
Study of Women's Health Across the Nation (SWAN), 1995–1997 (69)	2.11 (1.09–4.09)	3.62 (1.45–9.01)	NR

NR, not reported.
* Comparing type 2 diabetes versus no type 2 diabetes. All odds ratios were adjusted for body mass index.
SOURCE: References are listed within the table.

TABLE 28.20. Type 2 Diabetes and Risk of Incident Weekly Urinary Incontinence Among Women

STUDY, YEAR (REF.)	DURATION OF FOLLOW-UP	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	ADJUSTED RELATIVE RISK (95% CONFIDENCE INTERVAL)*
Nurses' Health Study (NHS), 1996–2000 (82)	4 years	47,461; NR	50–75	1.21 (1.02–1.43)
NHS, 2000–2002, NHS II, 2001–2003 (118)	2 years	71,650; 2,958	37–79	1.2 (1.0–1.3) Stress UI: 1.1 (0.9–1.4) Urgency UI: 1.4 (1.0–1.9) Mixed UI: 0.9 (0.7–1.3)
Study of Women's Health Across the Nation (SWAN), 1995–2002 (119)	6 years	1,529; NR	42–52	1.48 (1.06–2.07)

NHS, Nurses' Health Study; NR, not reported; UI, urinary incontinence.
* Comparing type 2 diabetes versus no type 2 diabetes. All relative risks were adjusted for body mass index in addition to other variables.
SOURCE: References are listed within the table.

TABLE 28.21. Type 2 Diabetes and Urinary Incontinence Improvement or Remission Among Women

STUDY, YEAR (REF.)	DURATION OF FOLLOW-UP	SAMPLE SIZE	OUTCOME	RESULT
Group Health Cooperative of Puget Sound (GHC), 1998–2002 (83)	1 year	672 with any UI	UI resolution	Prevalence: 14% in type 2 diabetes; 16% in no type 2 diabetes
Reproductive Risk factors for Incontinence Study at Kaiser (RRISK), 1999–2008 (85)	5 years	390 with at least weekly UI	Decrease in UI frequency	Unadjusted OR 0.46 (95% CI 0.15–1.40) comparing type 2 diabetes vs. no type 2 diabetes
Study of Women's Health Across the Nation (SWAN), 1995–2002 (86)	6 years	1,493 with at least monthly UI	Decreasing UI frequency from one annual visit to the next	Adjusted OR 0.91 (95% CI 0.77–1.07) comparing type 2 diabetes vs. no type 2 diabetes*

CI, confidence interval; OR, odds ratio; UI, urinary incontinence.
* Odds ratio adjusted for baseline body mass index, gain in weight, and waist-to-hip ratio over follow-up, in addition to other variables.
SOURCE: References are listed within the table.

TABLE 28.22. Type 2 Diabetes Characteristics and Urinary Incontinence Among Women

STUDY, YEAR (REF.)	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	TYPE 2 DIABETES CHARACTERISTIC	UI OUTCOME	MODEL COVARIATES	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)
Group Health Cooperative of Puget Sound (GHC), 1998–2002 (87)	1,017; 218	55–75	Duration	Prevalent severe UI*	Age, education, urinary tract infection in the past year	Referent: no type 2 diabetes <10 years: 1.4 (0.8–2.6) ≥10 years: 1.6 (0.7–3.4)
Nurses' Health Study (NHS), 1996–2000 (82)	81,845; 4,277	50–75	Duration	Prevalent weekly UI	Age, BMI, hormone therapy use, hysterectomy, low functional status, parity, race, smoking, stroke, waist-hip ratio	Referent: no type 2 diabetes <5 years: 1.13 (0.97–1.32) 5–10 years: 1.36 (1.17–1.57) >10 years: 1.34 (1.18–1.53)
NHS, 2000–2004, NHS II, 2001–2005 (71)	9,994; 9,994	37–79	Duration	Prevalent weekly UI	Age, BMI, diabetes medication use, diuretic use, hormone therapy use, hysterectomy, parity, physical activity, race, smoking	Referent: type 2 diabetes <5 years 5–10 years: 0.90 (0.79–1.03) >10 years: 1.17 (1.03–1.33)
Diabetes and Aging Study, 2005–2006 (63)	6,026; 6,026	30–75	A1c	Prevalent occasional UI	Age, BMI, comorbidity score, diabetes duration, diabetes treatment, education, income, parity, race	Referent: diabetes, A1c <6% A1c 6%–6.9%: 1.04 (0.95–1.14) A1c 7%–7.9%: 1.08 (0.99–1.19) A1c 8%–8.9%: 1.06 (0.96–1.18) A1c ≥9%: 1.09 (0.98–1.21)
GHC, 1998–2002 (87)	1,017; 218	55–75	A1c	Prevalent severe UI*	Age, education, urinary tract infection in the past year	Referent: no type 2 diabetes A1c ≤7.5%: 1.4 (0.7–2.6) A1c 7.6%–8.5%: 1.2 (0.4–3.0) A1c >8.5%: 1.2 (0.3–3.6)
GHC, 1998–2002 (87)	1,017; 218	55–75	Treatment	Prevalent severe UI*	Age, education, urinary tract infection in the past year	Referent: no type 2 diabetes Diet: 1.3 (0.5–2.8) Oral medication: 1.5 (0.8–2.9) Insulin: 1.7 (0.6–4.1)
Health, Aging, and Body Composition (Health ABC) Study, 1997–1998 (81)	1,584; 229	70–79	Treatment	Prevalent weekly urgency UI	Age, depressive symptoms, lower extremity physical function	Referent: no type 2 diabetes No medication: 1.02 (0.51–2.04) Oral medication: 1.78 (0.86–3.68) Insulin: 3.50 (1.55–7.91)
NHS, 2000–2004, NHS II, 2001–2005 (71)	9,994; 9,994	37–79	Treatment	Prevalent weekly UI	Age, BMI, diabetes medication use, diuretic use, hormone therapy use, hysterectomy, parity, physical activity, race, smoking	Referent: type 2 diabetes, no medication use Oral medication: 0.98 (0.87–1.10) Insulin: 1.03 (0.89–1.20)

TABLE 28.22. Type 2 Diabetes Characteristics and Urinary Incontinence Among Women (continued)

STUDY, YEAR (REF.)	SAMPLE SIZE (TOTAL; TYPE 2 DIABETES)	AGE (YEARS)	TYPE 2 DIABETES CHARACTERISTIC	UI OUTCOME	MODEL COVARIATES	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)
NHS, 1996–2000 (82)	47,461; NR	50–75	Microvascular complications	Incident weekly UI over 4 years	Age, BMI, hormone therapy use, hysterectomy, low functional status, parity, race, smoking, stroke, waist-hip ratio	Referent: type 2 diabetes, no microvascular complications 2.26 (1.32–3.87)
National Health and Nutrition Examination Surveys (NHANES), 2001–2002 (57)	246; 246	≥20	Neuropathic pain	Prevalent weekly UI	Age, albuminuria, BMI, hysterectomy, parity	Referent: type 2 diabetes, no neuropathic pain 2.37 (1.27–4.42)
GHC, 1998–2002 (83)	1,017; 218	55–75	Peripheral neuropathy	Prevalent any UI	Age, estrogen cream use, lifetime number of urinary tract infections, race, UI at the previous visit, vaginal discharge, vaginal dryness	Referent: no type 2 diabetes No: 0.8 (0.5–1.3) Yes: 1.7 (1.0–3.1)
GHC, 1998–2002 (87)	1,017; 218	55–75	Peripheral neuropathy	Prevalent severe UI*	Age, education, urinary tract infection in the past year	Referent: no type 2 diabetes No: 1.4 (0.7–2.7) Yes: 1.7 (0.9–3.2)
Action for Health in Diabetes (Look AHEAD), 2001–2004 (70)	2,994; 2,994	45–74	Diabetic retinopathy	Prevalent weekly urgency UI	Age, asthma, diastolic blood pressure, overall health status, sleep apnea, smoking, waist circumference	Referent: type 2 diabetes, no retinopathy 0.40 (0.19–0.86)
GHC, 1998–2002 (87)	1,017; 218	55–75	Diabetic retinopathy	Prevalent severe UI*	Age, education, urinary tract infection in the past year	Referent: no type 2 diabetes No: 1.1 (0.6–2.0) Yes: 1.9 (0.7–4.8)
NHANES, 2001–2002 (57)	246; 246	≥20	Albuminuria†	Prevalent weekly UI	Age, BMI, hysterectomy, neuropathic pain, parity	Referent: type 2 diabetes, no albuminuria Microalbuminuria: 0.98 (0.36–2.71) Macroalbuminuria: 3.82 (0.95–15.33)

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycosylated hemoglobin; BMI, body mass index; GHC, Group Health Cooperative of Puget Sound; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; UI, urinary incontinence.
* Severe UI was defined as weekly UI of amounts enough to moderately or completely wet underwear, wet outer clothes, or leak to the floor.
† Microalbuminuria was defined as urinary albumin-to-creatinine ratio of 30–300 mg/g. Macroalbuminuria was defined as albumin-to-creatinine ratio >300 mg/g.
SOURCE: References are listed within the table.

Poor glycemic control also has not been found to be associated with the odds of prevalent UI (Table 28.22). In the Diabetes and Aging Study, higher A1c was not associated with prevalence of occasional UI; however, among women with UI, higher A1c was related to more limitations in daily activities due to UI (adjusted OR 1.67, 95% CI 1.09–2.57 comparing A1c ≥9% vs. <6% [≥75 vs. <42 mmol/mol]) (63). The authors suggested that this finding may simply reflect a correlation between two indicators of diabetes severity (i.e., glycemic control and activity limitations), or it may indicate an association of poor glycemic control and glycosuria with exacerbation of preexisting UI (63). Longitudinal studies to evaluate whether changes in glycemic control predict changes in UI symptoms have not been conducted.

Data on diabetes treatment suggest a gradation of increasing UI frequency from no pharmaceutical treatment to insulin treatment (Table 28.22) (81,87); while treatment itself may be the causal factor or simply an indicator of diabetes severity and duration, these data suggest that health care providers might need to be more vigilant in assessing UI symptoms in patients receiving insulin treatment, since they appear to be a particularly high-risk group.

Several studies (57,82,83), but not all (87), have found strong associations between neuropathy or microvascular complications and the odds of UI. Among women with type 2 diabetes in the NHANES, the odds of prevalent weekly UI were over twofold higher in those with neuropathic pain (Table 28.22) (57). Existing data on diabetic retinopathy and albuminuria are too sparse to yield conclusions regarding their associations with UI.

UI IN WOMEN WITH TYPE 1 DIABETES

Urologic complications of type 1 diabetes are understudied. All information about UI in type 1 diabetes among women in the

TABLE 28.23. Prevalence of Urinary Incontinence in the Past 12 Months in Women With Type 1 Diabetes, UroEDIC, 2004

INCONTINENCE	PERCENT (N=550)
Frequency	
None	35
Less than monthly	28
Monthly	21
Weekly	13
Daily	4
Type*	
Any	23
Stress	22
Urgency	10

UroEDIC, ancillary study of urologic complications in the DCCT/EDIC cohort.
* Among women with incontinence during the previous 7 days.
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TABLE 28.24. Type 1 Diabetes and Odds of Prevalent Weekly Urinary Incontinence Among Women

URINARY INCONTINENCE OUTCOME	ADJUSTED PREVALENCE (%)*	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*
Weekly urinary incontinence		
Type 1 diabetes†	18.8	1.30 (0.90–1.88)
Normal glucose‡	15.1	Referent
Weekly stress urinary incontinence		
Type 1 diabetes†	18.5	1.47 (0.97–2.25)
Normal glucose‡	13.4	Referent
Weekly urgency urinary incontinence		
Type 1 diabetes†	8.8	2.05 (1.15–3.65)
Normal glucose‡	4.5	Referent

Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*.
* Prevalence and odds ratios were adjusted for age, body mass index, parity, hysterectomy, and current smoking.
† Data compare two study populations: women with type 1 diabetes examined by UroEDIC, an ancillary study of urologic complications in the DCCT/EDIC cohort, 2004, and women with normal glucose from the National Health and Nutrition Examination Surveys (NHANES) 2001–2002.
‡ Normal glucose was defined as fasting glucose <100 mg/dL.
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United States is derived from UroEDIC. Among these study participants, the prevalence of at least monthly UI during the past year was 38%, and the prevalence of weekly UI was 17% (Table 28.23) (88). The odds of prevalent weekly UI were 30% higher in women with type 1 diabetes in DCCT/UroEDIC compared with women in the NHANES 2001–2002 with fasting glucose <100 mg/dL, although the association was not statistically significant (Table 28.24) (60). Similar to type 2 diabetes, the ratio of stress to urgency UI was lower among women with type 1 diabetes (18.5:8.8) than in women with normal glucose levels (13.4:4.5), and the odds of urgency UI were particularly elevated in women with type 1 diabetes (60).

DIABETES TREATMENT AND PREVENTION OF UI

An analysis using data from the Diabetes Prevention Program (DPP) demonstrated the effectiveness of a low-fat diet and moderate-intensity physical activity intervention for decreasing type 2 diabetes incidence, as well as UI prevalence among overweight and obese women at risk of developing type 2 diabetes (89). Specifically, UI was measured at the end-of-trial visit using a self-administered questionnaire; the prevalence of weekly UI was significantly lower among women in the lifestyle intervention group compared with women in the groups receiving metformin treatment or placebo (38.3% vs. 48.1% vs. 45.7%, respectively, p=0.001; adjusted OR 0.76, 95% CI 0.61–0.95 comparing lifestyle intervention vs. placebo groups) (89). In analyses by UI type, the lifestyle intervention appeared to be associated with lower prevalence of weekly stress UI (adjusted OR 0.80, 95% CI 0.64–1.01 comparing lifestyle intervention vs. placebo groups), but not urgency UI. Almost all of the treatment effect was attributable to weight loss. Additionally, in a 6-year follow-up study of 1,778 women from the DPP, the prevalence of weekly UI had increased across the lifestyle intervention, metformin, and placebo groups but remained lower in the lifestyle intervention group (46.7% vs. 53.1% vs. 49.9%, respectively, p=0.03), indicating that the beneficial effects of the diet and exercise intervention extended years beyond the end of the trial (90). Overall, these data suggest that weight loss and lifestyle intervention may lower the risk of type 2 diabetes onset and promote remission of stress UI.

Similar to findings from the DPP in women at risk of type 2 diabetes, data from the Look AHEAD trial suggest that weight loss may be an effective strategy to specifically prevent stress UI in overweight and obese women with type 2 diabetes (91). After 1 year of follow-up, the incidence of weekly stress UI was lower in the intensive lifestyle intervention compared with the diabetes support and education group (10.5% vs. 14.0%; adjusted OR 0.60, 95% CI 0.39–0.91). This effect was explained mostly by differences in weight loss between the two groups.

In the DCCT/UroEDIC study, randomization to conventional versus intensive treatment for type 1 diabetes in the DCCT (mean follow-up 6.5 years) was not associated with prevalence of weekly UI assessed 10 years after the end of the trial (OR 1.24, 95% CI 0.79–1.96) (88). However,

management of diabetes was very good among women assigned to conventional treatment, and both groups had similar diabetes control during the decade following the trial, which might have affected the ability to detect an effect of intensive type 1 diabetes treatment on UI.

Overall, clinical trial evidence on UI treatment and prevention in women with type 1 or type 2 diabetes is scant. Further research is needed on the efficacy and safety of behavioral, pharmacological, and surgical treatments for UI in women with diabetes (92). In addition, studies are needed to evaluate the effects of standard diabetes treatment, standard UI treatment, and their combination on UI prevalence and incidence in women with diabetes or prediabetes (92).

ASYMPTOMATIC BACTERIURIA AND SYMPTOMATIC URINARY TRACT INFECTIONS IN WOMEN WITH DIABETES

Urinary tract infections (UTIs) are defined by pathogenic invasion of the urinary tract leading to inflammatory response of the urothelium (93). Asymptomatic bacteriuria (ASB) is the presence of bacteria in the urine that does not cause any symptoms (93). Although *Escherichia coli* is the most frequent bacterial cause of UTI in the general population of adult women (93), many patients with diabetes are infected with non-*Escherichia coli* species (94,95). In addition, among women with UTIs, those with type 1 or type 2 diabetes appear to have greater risk of infections progressing to complications or severe outcomes, such as abscess formation, renal papillary necrosis, bacteremia, and pyelonephritis, than those without diabetes (29). Although results have not been consistent, data from several epidemiologic studies suggest that ASB and symptomatic UTIs are more common in women with diabetes than in those without diabetes (96,97,98,99,100). However, many of these studies are not prospective cohorts and did not adjust for potential confounding factors, such as frequency of sexual intercourse.

Risk factors for UTI in women with diabetes are not well defined and may vary by type of diabetes. Women with both type 2 diabetes and ASB have an increased risk of developing symptomatic UTI compared with women with type 2 diabetes, but without ASB (94). Yet, a randomized clinical trial observed no association of screening and treatment of ASB episodes over 3 years with occurrence of symptomatic UTI in Canadian women with type 1 or type 2 diabetes and ASB (101). Also, similar to women without diabetes, sexual activity has been identified as the most important risk factor for UTI among women with type 1 diabetes (94,100,102). Thus, measures to prevent recurrent UTIs that have had success in women without diabetes (e.g., continuous or postcoital prophylaxis with low-dose antimicrobial agents and intermittent self-treatment with antimicrobials (103) might be considered for women with type 1 diabetes. Trials to assess the effectiveness of these strategies among women with type 1 diabetes have not been conducted.

SEXUAL DYSFUNCTION IN WOMEN WITH DIABETES

Female sexual dysfunction describes a departure from normal sensation and/or function during sexual activity, and includes dyspareunia, obstructed intercourse, vaginal laxity, and decreased sexual desire, arousal, or orgasm (50,104). Few studies have focused on sexual dysfunction in women with diabetes. Among existing studies, the majority are limited by small sample sizes, not including control women without diabetes, use of unidimensional measures of sexual function, or focusing on clinic or other nongeneralizable populations (105).

The RRISK 2 is one of the largest studies to compare sexual functioning in women with versus without diabetes. In this cross-sectional study of 2,270 women age 40–80 years, including 486 women with diabetes, sexual functioning in the past 3 months was assessed using

TABLE 28.25. Type 2 Diabetes and Odds of Sexual Dysfunction Among Women

OUTCOME	ADJUSTED ODDS RATIO (95% CONFIDENCE INTERVAL)*	
	Comparing Insulin-Treated Type 2 Diabetes vs. No Diabetes	Comparing Noninsulin-Treated Type 2 Diabetes vs. No Diabetes
Low sexual desire†	1.17 (0.79–1.72)	1.09 (0.85–1.42)
Low level of sexual arousal‡	1.19 (0.62–2.29)	1.09 (0.67–1.67)
Difficulty with lubrication§	2.37 (1.35–4.16)	1.01 (0.65–1.58)
Difficulty with orgasm‖	1.80 (1.01–3.20)	1.02 (0.65–1.58)
Pain or discomfort with intercourse¶	1.52 (0.76–3.06)	0.95 (0.56–1.62)

* Odds ratios adjusted for age; race or ethnicity; relationship status; history of sex with men, women, or both; parity; menopause status; hysterectomy; oophorectomy; body mass index; selective serotonin reuptake inhibitor use; and estrogen use. Low sexual desire was assessed in all participants regardless of sexual activity status, whereas low sexual arousal, difficulty with lubrication, difficulty with orgasm, and pain or discomfort with intercourse were assessed only in women reporting some sexual activity in the past 3 months.
† Women were considered to have low sexual desire if they reported that their level of sexual desire or interest was low, very low, or none.
‡ Women were considered to have "low sexual arousal" if they reported their level of sexual arousal during sexual activity was low, very low, or none.
§ Women were considered to have "difficulty with lubrication" if they reported it was difficult, very difficult, extremely difficult, or impossible to become lubricated during sexual activity.
‖ Women were considered to have "difficulty with orgasm" if they reported that it was difficult, very difficult, extremely difficult, or impossible to reach orgasm during sexual stimulation or orgasm.
¶ Women were considered to have pain or discomfort with intercourse if they reported their level of discomfort or pain during or after vaginal penetration was moderate, high, or very high.

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self-administered questionnaires with items derived from the Female Sexual Function Index (105,106). Among these women, those with insulin-treated type 2 diabetes versus no diabetes had a significantly higher prevalence of difficulty with lubrication (34% vs. 19%, p=0.003) and low sexual desire (62% vs. 53%, p=0.04) (105). After adjusting for a variety of potential confounding factors, women with insulin-treated type 2 diabetes were significantly more likely than women without diabetes to report difficulty with lubrication (OR 2.37, 95% CI 1.35–4.16) and difficulty with orgasm (OR 1.80, 95% CI 1.01–3.20) (Table 28.25). In addition, there were nonstatistically significantly elevated odds of pain or discomfort with intercourse among women with insulin-treated type 2 diabetes versus women without diabetes (OR 1.52, 95% CI 0.76–3.06) (Table 28.25) (105). Odds of low sexual desire and low level of sexual arousal were not significantly different between women with insulin-treated type 2 diabetes or noninsulin-treated type 2 diabetes and women without diabetes (Table 28.25). In contrast, other studies of middle-aged and older women have not observed associations between diabetes and sexual dysfunction (107,108,109). For example, among 1,550 women age 57–85 years, self-reported diabetes diagnosis was not associated with any self-reported sexual problem lasting several months or more during the past year, including difficulty with lubrication (OR 0.94, 95% CI 0.50–1.76) or pain during intercourse (OR 0.83, 95% CI 0.44–1.59) (107); however, unlike in the RRISK 2 study, women with more severe diabetes were not separately examined.

Very little is known about sexual dysfunction among women with type 1 diabetes. One study of 424 women with type 1 diabetes (mean age 43 years) in UroEDIC found a 35% prevalence of sexual dysfunction, defined based on a cutoff score of 22.75 on an abbreviated version of the Female Sexual Function Index (110). Common complaints among women meeting the criteria for sexual dysfunction were decreased desire (57%), problems with orgasm (51%), inadequate lubrication (47%), problems with sexual arousal (38%), and pain during intercourse (21%) (110); the study did not include a comparison group of women without type 1 diabetes.

Several mechanisms, including psychological factors, diabetes complications, and medication use, may explain a higher prevalence of sexual dysfunction in women with diabetes than those without diabetes. Depression, a common condition in adults with diabetes (111), was found to be significantly associated with decreased arousal (OR 2.47, 95% CI 1.31–4.66) and inadequate lubrication (OR 2.41, 95% CI 1.33–4.37) in women in UroEDIC with type 1 diabetes (110). Moreover, antidepressant use may lead to new onset or worsening of sexual dysfunction (112). Complications of diabetes, such as neurovascular dysfunction leading to suboptimal pelvic blood flow and damage to large sensory fibers, may also contribute to higher frequency of decreased sexual arousal in women with diabetes. In addition, vaginal infections and decreased vaginal lubrication, which are more common in women with than without diabetes, may contribute to sexual pain. Sexual dysfunction may also occur as an adverse effect of medications used for conditions commonly comorbid with diabetes, such as hypertension, and high cholesterol (113). Although nonpharmacologic and pharmacologic treatment options for sexual dysfunction are available (113), their effectiveness or appropriateness specifically among women with diabetes is largely unknown. Clearly, much remains to be learned regarding prevalence, prevention, and treatment of sexual dysfunction among women with diabetes.

CONCLUSION

Although urologic complications are common and major health problems in men and women with diabetes, data to define expected prevalence, incidence, and risk factors, as well as interventions to reduce the risk of developing these complications, are limited. It is well recognized that intensive glycemic control delays the onset and progression of microvascular complications in both type 1 and type 2 diabetes. If microvascular complications also damage the vascular and neurologic innervation of the urethral sphincter, bladder, and corpora cavernosa, then intensive glycemic control may prevent or improve the severity of urologic complications.

In summary, future research is needed to identify the magnitude of onset and progression of urologic complications associated with diabetes, elucidate mechanisms by which diabetes exerts its effects on these complications, and identify the most effective treatment and prevention strategies for urologic complications associated with diabetes to reduce the psychosocial, medical, and economic costs of these highly prevalent and chronic disorders affecting men and women.

LIST OF ABBREVIATIONS

A1c. . . . . .glycosylated hemoglobin
ASB . . . . . .asymptomatic bacteriuria
AUASI . . . . . .American Urological Association Symptom Index
BACH. . . . . .Boston Area Community Health survey
BLSA . . . . . .Baltimore Longitudinal Study of Aging
BMI . . . . . .body mass index
BPH. . . . . .benign prostatic hyperplasia
CI. . . . . .confidence interval
DCCT. . . . . .The Diabetes Control and Complications Trial
DISTANCE . . . .Diabetes Study of Northern California
DPP . . . . . .Diabetes Prevention Program
ED . . . . . .erectile dysfunction
EDIC . . . . . .Epidemiology of Diabetes Interventions and Complications
FMHS. . . . . .Flint Men's Health Study
GHC. . . . . .Group Health Cooperative of Puget Sound
Health ABC . . .Health, Aging, and Body Composition Study
HERS. . . . . .Heart and Estrogen/progestin Replacement Study
HPFS . . . . . .Health Professionals Follow-Up Study
HRS . . . . . .Health and Retirement Study
IGF. . . . . .insulin-like growth factor
IIEF . . . . . .International Index of Erectile Function
Look AHEAD . .Action for Health in Diabetes
LUTS . . . . . .lower urinary tract symptoms
MARSH . . . . . .Male Attitudes Regarding Sexual Health Survey
MMAS . . . . . .Massachusetts Male Aging Study
NHANES . . . . .National Health and Nutrition Examination Survey
NHS. . . . . .Nurses' Health Study
OAB . . . . . .overactive bladder
OCS . . . . . .Olmsted County Study of Urinary Symptoms and Health Status in Men
OR . . . . . .odds ratio
RRISK . . . . . .Reproductive Risk factors for Incontinence Study at Kaiser
SWAN . . . . . .Study of Women's Health Across the Nation
UI. . . . . .urinary incontinence
UroEDIC. . . . . .ancillary study of urologic complications in the DCCT/EDIC cohort
UTI. . . . . .urinary tract infection

CONVERSIONS

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions.*

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DUALITY OF INTEREST

Drs. Sarma, Townsend, Grodstein, Breyer, and Brown reported no conflicts of interest.

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