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Autonomic Neuropathy and Urologic Complications in Diabetes

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Abstract

Urological complications in diabetes mellitus are very common; in fact, genitourinary complications are more common than diabetic neuropathy or nephropathy. These complications consist of sexual and urinary dysfunction, greatly impact quality of life, and result in increased morbidity. Diabetic autonomic neuropathy affects the entire autonomic nervous system and can lead to dysfunction of the cardiovascular, gastrointestinal, and genitourinary organ systems. Genitourinary dysfunction associated with diabetic autonomic neuropathy includes diabetic bladder dysfunction, sexual dysfunction, and recurrent urinary tract infections. While several studies have reported on genitourinary dysfunction in individuals with diabetes, UroEDIC, an ancillary study to the Diabetes Control and Complications Trial (DCCT) and its observational follow up, the Epidemiology of Diabetes Interventions and Complications study (EDIC), comprehensively characterized urologic complications in the cohort and examined the association between cardiovascular autonomic neuropathy and sexual and urinary dysfunction. UroEDIC demonstrated significant associations between autonomic neuropathy and urologic complications in type 1 diabetes, specifically erectile dysfunction, female sexual dysfunction, and lower urinary tract symptoms. In this narrative review, we review the current literature on urological complications in diabetes.

Keywords

Diabetes; Autonomic Neuropathy; Bladder Dysfunction; Erectile Dysfunction; Sexual Dysfunction

1. Introduction

Diabetic autonomic neuropathy (DAN), is a serious and common complication often identified in patients with type 1 diabetes mellitus (T1DM) (Pop-Busui et al., 2017a). Autonomic neuropathy in diabetes mellitus (DM) has a significant impact on morbidity, mortality, and quality of life. DAN often involves and affects the entire autonomic nervous system, and dysfunction can present in the major organ systems including cardiovascular, gastrointestinal, and genitourinary (Pop-Busui et al., 2017a). DAN may be isolated or

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coexist with other peripheral neuropathies and other diabetic complications. In isolation, it frequently precedes the detection of other complications (Thompson et al., 2005, Gandaglia et al., 2013).

The genitourinary complications associated with DAN contributes to various disorders including bladder and sexual dysfunction (Pop-Busui et al., 2017a). These urologic complications occur frequently in both men and women living with T1DM (Wessells, 2013, Brown et al., 2005) and type 2 diabetes (T2DM) (Sayyid and Fleshner, 2016, Kouidrat et al., 2017) and are associated with significant reductions in health related quality of life above and beyond other diabetic complications (Jacobson et al., 2015). In this article, we discuss the epidemiology, clinical presentation, risk factors and gaps in knowledge based on a detailed review of peer reviewed publications of autonomic dysfunction in diabetes impacting the genitourinary system. We also present a summary of current findings from UroEDIC, an ancillary study examining urologic complications of diabetes among participants from the Diabetes Control and Complications Trial (DCCT) and its observational follow up, the Epidemiology of Diabetes Interventions and Complications study (EDIC) (Wessells et al., 2018). Given the unparalleled, comprehensive phenotyping of this large T1DM cohort for all complications and risk factors, UroEDIC provides the best insight into the association between DAN and urological complications.

2. Autonomic Dysfunction in Diabetes

The autonomic nervous system controls several organ systems in the body, including the cardiovascular, gastrointestinal, and urogenital organ systems. Chronic hyperglycemia associated with diabetes is largely responsible for damage to small nerve fibers, resulting in diabetic autonomic neuropathy (DAN). DAN is a subtype of the peripheral polyneuropathies that accompany diabetes (Pop-Busui et al., 2017a).

Major clinical manifestations of DAN include resting tachycardia, exercise intolerance, orthostatic hypotension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, and hypoglycemic autonomic failure (Pop-Busui et al., 2017a). Signs and symptoms related to DAN typically do not occur until long after the onset of diabetes and vary greatly from asymptomatic to severe, and relate to the specific affected end organ systems. Subclinical DAN can occur within a year of diagnosis of diabetes (Pfeifer et al., 1984). Given the association of DAN with adverse cardiovascular outcomes, such as cardiovascular deaths, cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN (Pop-Busui et al., 2010, Pop-Busui et al., 2017a, Pop-Busui et al., 2017b). Noninvasive testing of CAN allows for extensive clinical and epidemiologic investigation. CAN has widespread early effects in the progression of DAN (Ziegler, 1994). In many studies, including those from UroEDIC, CAN is the surrogate measure of DAN. Reduced heart rate variation is the earliest indicator of CAN (Ziegler, 1999), and is an integral measure used to characterize CAN in UroEDIC participants.

3. Genitourinary Dysfunction in Diabetes

The World Health Organization (WHO) estimated that in 2014, of 422 million people worldwide living with diabetes (Roglic, 2016), 25-90% had diabetic uropathy, a complication that is more common that neuropathy or nephropathy (Panigrahy et al., 2017, Daneshgari and Moore, 2006). Diabetic uropathy has been recognized since 1935. The spectrum of diabetic uropathy consists of diabetic bladder dysfunction, sexual dysfunction, and recurrent urinary tract infections. Dysfunctional nerves in the lower spinal cord, from DAN, can cause urinary dysfunction. This dysfunction can present as decreased bladder sensation, incomplete emptying, urinary urgency, and urinary incontinence (Vinik et al., 2003) which can then lead to urinary tract infections. The impact of neuropathy on vascular tone and sympathetic autonomic response can also lead to erectile dysfunction and female sexual dysfunction (Thorve et al., 2011, Enzlin et al., 1998, Pop-Busui et al., 2015, Hotaling et al., 2016). Though not life- threatening, these symptoms have a major impact on quality of life and can result in increased morbidity (Hill et al., 2008).

4. DCCT/EDIC and UroEDIC

The DCCT and EDIC studies have been described in detail previously (Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group, 1999, Molitch et al., 1993, Nathan et al., 2003). Briefly, the DCCT included 1,441 subjects with T1DM for 1-15 years with no (primary prevention cohort) or minimal diabetic retinopathy (secondary intervention cohort). Subjects were randomly assigned to either intensive or conventional treatment and were followed for 3-9 years (mean 6.5 years) (Molitch et al., 1993). The trial was terminated early in 1993 when intensive therapy was recommended for all subjects. In 1994, 96% of the original DCCT cohort agreed to participate in EDIC, which included annual examinations for complication status. Annual EDIC examinations began in 1994, with 1,375 (96%) DCCT subjects consenting to participate in EDIC. The mean age of the participants at EDIC baseline was 33.6 years with a mean duration of diabetes of 12.2 years. All men and women enrolled in EDIC were invited to participate in UroEDIC, an ancillary study designed to examine urologic complications of diabetes.

4.1 Urological Complications Evaluations in UroEDIC

This included the first standardized and validated assessments of ED, FSD, LUTS and UI in 2003 (EDIC year 10, UroEDIC baseline), 2010 (EDIC year 17, UroEDIC II), and annually thereafter. (Describe the measurements here…) in detail then remove from later paragraphs where you can discuss just findings

4.2 Cardiovascular Autonomic Neuropathy Evaluations in DCCT/EDIC (Braffett et al., 2016)

Standardized and rigorous CAN evaluations were established as part of DCCT.(put above ref here?) These included cardiovascular autonomic reflex tests, which assessed R-R response to paced breathing (R-R variation), Valsalva maneuver, and postural changes in blood pressure measured at baseline, biennially during DCCT, and at years 13/14 and 16/17 during EDIC (The Diabetes Control and Complications Research Trial Group, 1998, Pop-

Busui et al., 2009). These cardiovascular reflex tests are objective, highly reproducible and recommended by consensus in the field as the gold-standard (Spallone et al., 2011). The standardized cut points for CAN measures used in DCCT included R-R variation<15 and Valsalva ratio≤1·5. Abnormal CAN function was defined as: either R-R variation<15 or R-R variation between 15-19·9 *plus* either a Valsalva ratio ≤1·5 or a supine-to-standing drop of 10 mm Hg in diastolic blood pressure (Pop-Busui et al., 2009).

5. Diabetic Bladder Dysfunction

Diabetic bladder dysfunction (DBD) is the most common genitourinary complication of diabetes (Daneshgari et al., 2009). Afferent nerve impulses of bladder sensation and reflex bladder contraction are carried by sympathetic, parasympathetic, and somatic afferent and efferent nerves of the spinal cord. Bladder autonomic dysfunctions, therefore include sensory abnormalities resulting in insensate bladder, which leads to an elevated threshold (post void residual) to initiate the micturition reflex, then leading to increased bladder capacity and urinary retention (Blaivas, 1982). Damage to efferent parasympathetic fibers from DAN can cause symptoms including weak steam and dribbling, with detrusor areflexia. DBD is an umbrella description representing progressive clinical symptoms of storage and voiding bladder problems (Liu and Daneshgari, 2014). The presentation of diabetic bladder dysfunction varies based on gender, age, concurrent voiding problems, and diabetes duration (Esteghamati et al., 2007). Early stages include storage problems, such as urinary frequency, urgency, and urge incontinence (Daneshgari et al., 2009), and symptoms consistent with overactive bladder (OAB). This can then progress to insensate, decompensated bladder characterized by overflow incontinence, urinary retention, and increased post-void residual volumes also known as “diabetic cystopathy” (Yuan et al., 2015).

Diabetic cystopathy is also referred to as neurogenic bladder and is presumed to represents later stage bladder dysfunction attributed to DAN (Gomez et al., 2011). Changes in detrusor physiology, neuronal impairment, and urothelial dysfunction are the major factors which contribute to diabetic cystopathy (Gomez et al., 2011). Unlike other sequelae of DAN, the pathogenesis of diabetic bladder dysfunction results from the impact of both hyperglycemia and polyuria. Hyperglycemia induces oxidative stress (Rolo and Palmeira, 2006), which can damage smooth muscle cells and induce cell apoptosis leading to accelerated neurodegeneration in the diabetic bladder (Kanika et al., 2011, Whitmire et al., 2011). Polyuria leads to an adaptation to diuresis including bladder wall remodeling, thereby altering bladder function in diabetic persons (Liu and Daneshgari, 2006, Daneshgari et al., 2006).

The most common, classic urodynamic findings in individuals with diabetic bladder dysfunction are insensate bladder, increased post void residual volume, and decreased detrusor contractility (Wittig et al., 2019). Recent clinical studies have demonstrated these classic findings and emphasized that patients can often present with a mixed clinical picture. Table 1 reviews studies describing associations between neuropathic complications and bladder dysfunction in both men and women. A study by Ueda et al. evaluated asymptomatic diabetic patients. In this study, increased bladder volume at first sensation to void, decreased detrusor contractility, and increased post void residual volumes were

observed in asymptomatic diabetic patients. This study, however, also noted a 25% incidence of detrusor overactivity, consistent with early stages of diabetic bladder dysfunction (Ueda et al., 2000). Large scale studies of urinary incontinence have demonstrated a 30-70% increased risk of overall incontinence with diabetes, with a 50% increase risk of urge incontinence in women (Brown et al., 1996). A study evaluating 1359 patients with diabetes, demonstrated that 23% of diabetic patients had overactive bladder; of these 48% had urinary incontinence (Liu et al., 2011).

Bladder dysfunction in diabetes is an important complication of diabetes and can start at an early stage; neuropathy is an explanation for the asymptomatic presentation of many patients as it can lead to an insensate bladder. The urothelium has an important sensor controlling bladder function. The bladder urothelium may also contribute to the decreased sensation in those with diabetic bladder dysfunction owing to reactive oxidative damage (Fedele, 2005).

5.1. Diabetic Bladder Dysfunction in Women

Women with diabetes suffer from a high rate of urinary incontinence. A recent survey demonstrated that 43% of women aged 50-64 and 51% of women aged 65-80 report urinary incontinence. Of these, 31% of women reported daily leakage episodes (Swenson C, November 2018). The Nurses' Health Study, which examined 14,286 nurses, reported that women with DM were at significantly greater risk of prevalent incontinence, which was more marked for larger volumes of leakage. Greater risk of incontinence was associated with longer duration of DM. Women with type 2DM for over 10 years had an almost 50% risk of incontinence (Lifford et al., 2005). A study of 7949 women over the age of 65, demonstrated that those with DM were at greater risk of daily incontinence. The Diabetes Control and Complications Trial (DCCT) and its observational follow up, the Epidemiology of Diabetes Interventions and Complications study (EDIC) (Brown et al., 1999). In addition, a study of 1500 women aged 70-79 demonstrated a risk of urge incontinence in women with DM on insulin, demonstrating an association of DM severity and incontinence (Diokno et al., 1990). These studies are based on self-reported symptoms and may in effect, underestimate the risk of incontinence associated with DM.

Women also demonstrate other manifestations of diabetic bladder dysfunction. Lee et al. evaluated the effects of diabetes on voiding behavior in a cross-sectional study of 194 female patients with diabetes; a comparison with 162 nondiabetic controls was done. Confounding factors, such as neurological disorders and aging were eliminated. Voiding was evaluated with the American Urological Association Symptom-Index (AUA-SI) questionnaire, in addition to uroflowmetry and post void residual urine volume (Lee et al., 2004). Compared to controls, women with diabetes had more nocturia, weaker urinary streams, less voided volumes, and lower maximal flow rates. High residual urine (≥100ml) was demonstrated in 13.9% of participants, compared to 1.8% of controls. Female gender has also been associated with increased bladder capacity (Esteghamati et al., 2007). A study of 400 women with type 2 Diabetes demonstrated that women with poor glycemic control (as measured by Hemoglobin A1C greater than 8.4) are more likely to develop urinary retention than those with proper glycemic control (Tai et al., 2016). This study also evaluated the impact of diabetic neuropathy on lower urinary tract symptoms in women, and showed that peripheral

diabetic neuropathy, not Hemoglobin A1C, was a significant predictor of lower urinary tract symptoms in women with DM.

5.2. Diabetic Bladder Dysfunction in Men

Male gender is associated with decreased bladder compliance and bladder outlet obstruction. Moreover, although benign prostatic hyperplasia (BPH) and diabetes have significant overlap in voiding symptoms, there is evidence that diabetes promotes the disease process of BPH (Gomez et al., 2011). The proposed mechanism is through the increased sympathetic tone of the prostate through high insulin levels. High insulin levels then increase sympathetic nerve activity and stimulate prostate growth (Parsons et al., 2006, Rohrmann et al., 2005, Sarma et al., 2009).

In men, lower urinary tract symptoms (LUTS), including straining, intermittency, postvoid dribbling, and weak stream can be attributed to benign prostatic hyperplasia (BPH) and diabetes. There is significant overlap, which is demonstrated by Kaplan et al, who studied diabetic men and showed that 57% of men with diabetes and LUTS had bladder outlet obstruction on urodynamics (Kaplan et al., 1995). Similar symptoms can be seen from urethral obstruction from BPH, and may also result from bladder dysfunction due to denervation and poor detrusor contractility. It is important to differentiate the clinical overlap of BPH and OAB. Men with diabetes may also have detrusor overactivity secondary to microvascular complications, which can also cause symptoms consistent with OAB including urinary urgency, frequency and nocturia. Several studies suggest that men with diabetes report increased frequency of LUTS with an estimated 25% to nearly twofold-increased risk of LUTS in men with diabetes (Sarma AV, Joseph et al., 2003, Michel et al., 2000a). Michel et al demonstrated in a large cohort of men with clinically diagnosed BPH, 13% of men with diabetes had worse LUTS and lower flow rate (Michel et al., 2000b). In addition, among men with BPH, diabetes is associated with increased LUTS compared to nondiabetic men (Michel et al., 2000a).

5.3. Diabetes and Urinary Tract Infections

Compared to individuals without diabetes, those with diabetes have an increased risk of UTI (Boyko et al., 2005, Chen et al., 2009). Epidemiological studies suggest that both asymptomatic bacteriuria and symptomatic UTIs may occur with more frequency in women with DM (Stapleton, 2002, Zhanel et al., 1995, Geerlings et al., 2000b). Women with DM have a 2-3 fold higher prevalence of asymptomatic bacteriuria and are at higher risk of symptomatic infection. While woman with type 2 DM and asymptomatic bacteriuria are at increased risk of symptomatic UTI (Geerlings et al., 2000a), those with T1DM and asymptomatic bacteriuria are at increased risk of pyelonephritis and impaired renal function (Geerlings et al., 2001). The increased risk of asymptomatic bacteriuria and symptomatic UTI is due to several mechanisms including glucosuria which can promote bacterial growth, immunosuppression and elevated postvoid residual or incomplete emptying (Hill et al., 2008, Chen et al., 2009). UTI risk increases with disease duration and severity (Gomez et al., 2011). In addition, Escherichia coli expressing type 1 fimbriae have increased adherence to the urothelium of diabetic patients. An analysis of 456,586 patients with diabetes demonstrated that UTI risk was associated with high Hemoglobin A1C values in

the previous year and poor kidney function (Wilke et al., 2015). Older women with diabetes and previous UTI are also at greater risk of UTI.

5.4 Findings from UroEDIC

Bladder Dysfunction Evaluations in UroEDIC (Braffett et al., 2016)—LUTS severity in men was determined with the American Urological Association Symptom Index (AUASI), a standardized seven-item questionnaire (Barry et al., 1992). Scores range from 0 to 35 with 8-35 indicating the presence of LUTS (8-19 moderate, 20-25 severe) (Barry et al., 1992). Urinary incontinence in women was determined based on incontinence frequency and amount of urine lost per episode (drops, small splashes, more), using the validated Sandvik Severity Index (Sandvik et al., 1995). The Sandvik Severity Index is calculated from frequency and amount of urine loss on a scale of 0 to 12 (dry/mild – 0 to 2, moderate – 3 to 6, severe – 8 to 9, very severe – 12) with scores 3 to 12 indicating moderate/very severe UI.

UroEDIC has evaluated the effect of glycemic control on urologic complications, including urinary incontinence and urinary tract infections.

A UroEDIC study of 64 women with Type 1 Diabetes demonstrated that mean EDIC HbA1C was associated with increased odds of urinary incontinence (Lenherr et al., 2016b). Poor glycemic control was also associated with higher frequency of urinary tract infections (Lenherr et al., 2016a). In examining urologic complications at EDIC year 10 (UroEDIC I) and EDIC year 17/18 (UroEDIC II) (Wessells et al., 2018), most participants who had a urological complication at UroEDIC I had persistence of the same complication at UroEDIC II. The one exception was UTI in females, which was noted to have lower prevalence at UroEDIC II (29% who reported UTI at UroEDIC 1 also had UI at UroEDIC II).

6. Sexual Dysfunction in Diabetes

Impaired sexual function is a common complication of diabetes in men and women. Many studies have focused on erectile dysfunction (ED) in men, but it is important to note that women can also present with sexual dysfunction (Tamas and Kempler, 2014). Sexual dysfunction in both sexes is associated with depression and diminished quality of life. Table 2 reviews studies describing associations between neuropathic complications and sexual dysfunction in both men and women.

6.1. Female Sexual Dysfunction

Female sexual dysfunction (FSD) encompasses dyspareunia, vaginal laxity, and decreased sexual desire, arousal, or orgasm (Basson et al., 2000, Haylen et al., 2010). These are also symptoms that have been reported with higher frequency in women with T1DM and T2DM (Aslan and Fynes, 2008, Enzlin et al., Fatemi and Taghavi, 2009). The Female Sexual Function Index (FSFI) was established to provide a valid, reliable instrument to assess key domains of female sexual function, including desire, arousal, lubrication, orgasm, satisfaction and pain, and is the scale used to evaluate female sexual function (Rosen et al., 2000).

In the DCCT cohort, depression and marital status were predictors of sexual dysfunction in women. Similar findings were observed in women with T2DM (Nowosielski et al., 2010). A recent study of sexual function in 145 women with T1DM and compared them to controls. In addition, this study evaluated the impact of insulin delivery method on the prevalence of sexual dysfunction. This study demonstrated that young women with T1DM and insulin pump had similar prevalence of sexual dysfunction compared to health age- matched women (Maiorino et al., 2017). Those on multiple daily injections, however, had significantly impaired sexual function compared to health age-matched women. In this study, similar to previous studies, depression and mental health status were independent predictors of FSD in diabetic women. Despite the higher prevalence of sexual dysfunction among diabetic women, in these studies, no strong association was found with diabetes related factors, such as glycemic control and complications of diabetes. With this, many conclude that female sexual dysfunction in diabetic patients, as in patients without diabetes (Laumann et al., 1999), are more psychogenic in nature (Giraldi and Kristensen, 2010). This would imply that women with diabetes have more psychological sequelae, potentially from their disease burden. Unlike research in male sexual dysfunction, research in female sexual dysfunction, however, is significantly limited leading to less conclusive than those of studies in men (Enzlin et al., 1998).

Studies on female sexual dysfunction in diabetes have been limited by small sample size, inadequate characterization of diabetes, particularly with regard to glycemic control, neurovascular complications, psychological adjustment to diabetes, and presence or absence of comorbid depression (Enzlin et al., 1998) A recent study evaluated the relationship of sexual dysfunction with depression and acceptance of illness in women and men with T2DM. There were 114 women with T2DM and 183 controls (Bak et al., 2017). The FSFI was used in women, this study found 68% prevalence of FSD compared to 17% in controls. Patients with DM had higher scores on the Beck Depression Inventory (BDI), which negatively correlated with point values on the FSFI. This study concluded that sexual dysfunction in diabetic women is correlated with depression and acceptance of their illness.

The contribution of DAN to female sexual dysfunction is less well-established. It is likely that disruption of the autonomic nervous system, which contributes to major components of sexual function, is a driver of dysfunctions in certain domains of female sexual function, such as arousal and orgasmic function.

6.2. Male Sexual Dysfunction

Male sexual function is often impaired in diabetes. The majority of studies of sexual function in men have focused on ED. However, male sexual dysfunction encompasses abnormalities of orgasmic, ejaculatory function, desire/libido and erectile function (Penson et al., 2009). Burke et al. demonstrated that the presence of diabetes was significantly associated with all aspects of sexual function and sexual satisfaction (Burke et al., 2007).

Erectile dysfunction is as a man’s consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity,(NIH Consensus Conference,1993) and has been found to be an age-related disease that affects 20% of men over the age of 40 years. ED is thought to be a surrogate marker for both diabetes and cardiovascular disease and has

been shown to be the first sign of diabetes, diagnosed in 12-30% of men who initially present with ED (Lewis, 2001, Sairam et al., 2001, Gur et al., 2014)· Up to 75% of men with diabetes have ED, with diabetic men being affected at a younger age (Kouidrat et al., 2017). A meta-analysis of 145 studies, estimates the overall prevalence of ED at 52.5%, 37.5% for T1DM and 57.7% for T2DM. A study demonstrated that compared to controls without diabetes, those with diabetes were at increased odds of having ED (OR 3.56; 95 CI 2.54-5.16). In men with diabetes, ED not only occurs earlier than in the normal population, but it is also less responsive to oral pharmacological therapy (Feldman et al., 1994). ED has a multifactorial pathophysiology and can occur concurrently with vasculopathy, neuropathy, and depression (Lizza and Rosen, 1999, Kouidrat et al., 2017). DAN is an important factor in the development of diabetes associated ED and DAN affects neural systems at all levels of tumescence and rigidity. Mechanistically, diabetes can impair endothelial relaxation leading to ED. Studies have demonstrated impairment in the initial stage of tumescence, with impaired non-adrenergic-non-cholinergic (NANC) nerve endings and neuronal nitric oxide synthase (nNOS) activation and NOS release (Hidalgo-Tamola and Chitaley, 2009).

6.3. Findings from UroEDIC

Sexual Dysfunction Evaluations in UroEDIC (Braffett et al., 2016)—Presence of ED in men was initially assessed with the validated International Index of Erectile Function (IIEF) (Rosen et al., 1997). ED was then ascertained based on a single question from the IIEF: *In the last 4 weeks, how would you rate your confidence to get and keep an erection?* This single question had been shown in DCCT/EDIC studies to strongly correlate with the IIEF erectile function domain composite score. In addition, it was shown to correlate well with bother due to erectile problems and global sexual bother, and thus serves as a proxy for global sexual function and bother (Penson et al., 2009). A separate question queried use of oral medications and/or erectile aids/devices of all participants. Those who reported any use were categorized as having ED. FSD was evaluated by the abbreviated version of the Female Sexual Function Index (FSFI-R), a widely used, well-validated, multi-dimensional, self-report measure that assesses sexual function across six domains including sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. Presence of FSD was defined by a score ≥22.75 on the FSFI-R (Rosen et al., 2000).

Female Sexual Dysfunction in UroEDIC—The overall prevalence of FSD at EDIC year 10 (UroEDIC I) was 35.4%. Though biivariate analysis demonstrated that women with FSD were more likely to have evidence of microvasculopathy, multivariable analysis demonstrated that only depression status and marital status were predictors of FSD (Enzlin et al., 2009). Women with depression had 2.08 higher odds of FSD than women who were not depressed, and married women had 2.49 higher odds of FSD than unmarried women. UroEDIC also evaluated the association between measures of CAN with FSD and UI among female UroEDIC participants (Hotaling et al., 2016). This study demonstrated that CAN was significantly more prevalent among women with FSD and/or UI; 41% and 44% of women with FSD and UI, respectively, had positive measures of CAN compared to 30% and 38% of women without FSD or UI. Similar associations were observed between CAN and UI at EDIC year 13/14. In multivariable analyses adjusting for known risk factors such as age, BMI, post-menopausal status, parity, smoking, alcohol consumption, HbA1c, SBP,

duration of diabetes, and beta blocker use, lower R-R variation at EDIC year 16/17 were associated with significantly increased odds of FSD and Valsalva ratio ≤1.5 was associated with increased odds of UI at EDIC year 13/14. Although autonomic dysfunction has been considered to be an important factor in the etiology of many diabetic complications, this study is among the first to systematically demonstrate a link between CAN and FSD in a large cohort of well-characterized patients with T1DM (Vinik et al., 2003).

Erectile Dysfunction in UroEDIC—UroEDIC examined the association between CAN and ED and LUTS in a large cohort of male participants with T1DM in the DCCT/EDIC study and found that the prevalence of an abnormal composite CAN was higher in participants with ED or LUTS compared with those without ED or LUTS ($p<0{\cdot}0001$) (Pop-Busui et al., 2015). In multivariable analysis, participants with CAN had 2.65 greater odds of ED and LUTS (95% CI=1.47,4.79). This strong association between CAN, ED and LUTS suggests that CAN may be a useful surrogate biomarker of not only more generalized autonomic neuropathy, but also may predict the development of ED and LUTS in men with long-standing T1DM. These findings are the first to systematically demonstrate a link between CAN and ED/LUTS in a large cohort of well-characterized men with T1DM. In evaluating other male sexual dysfunctions, we have demonstrated that participants with Orgasmic Dysfunction and ED had 2.89 higher odds of CAN and 2.28 higher odds of peripheral neuropathy as measured by the Michigan Neurological Screening Instrument (MNSI).

Persistence of urologic complications in UroEDIC—UroEDIC recently examined urologic complications at EDIC year 10 (UroEDIC I) and EDIC year 17/18 (UroEDIC II) and demonstrated that most participants who had a urological complication at UroEDIC I had persistence of the same complication at UroEDIC II (Wessells et al., 2018) (Figure 1). For women, the prevalence of FSD at UroEDIC II was highest at 42%, and for men, the prevalence of ED was highest at 45%. The important factor in this study was that though there was persistence of many urological complications, there was a subset of participants in which there was remission of symptoms. As demonstrated in Table 3, women with autonomic neuropathy at UroEDIC II had 1.67 higher odds of FSD (95%CI= 1.07,2.60) and 1.57 higher odds of UTI (95%CI= 1.00,2.47). In men, those with autonomic neuropathy at UroEDIC II had 2.07 higher odds of LUTS (95%CI=1.42, 3.01), 2.82 higher odds of ED (95%CI= 2.01, 3.94), and 2.40 higher odds of Orgasmic Dysfunction (95%CI=1.49, 3.88).

7. Conclusions

Urological complications of diabetes appear to be strongly associated with diabetic autonomic neuropathy. The influence of glycemic control in DM on these complications is important given the link of occurrence of these complications with increasing diabetes severity. In men and women with long-standing diabetes, CAN may be a predictor of ED and LUTS and FSD and UI respectively. Though it is not possible to reverse neuropathy once it occurs, understanding long term, downstream effects of autonomic neuropathy on organ systems including the genitourinary system is important. An increased understanding can potentially lead to patients taking control of their diabetes to prevent or delay further nerve damage. Additional large-sample longitudinal studies are needed

to evaluate the association and progression of urogenital complications as a function of autonomic dysfunction in diabetes and to identify treatment strategies to reduce the burden and psychosocial consequences of CAN on genitourinary complications.

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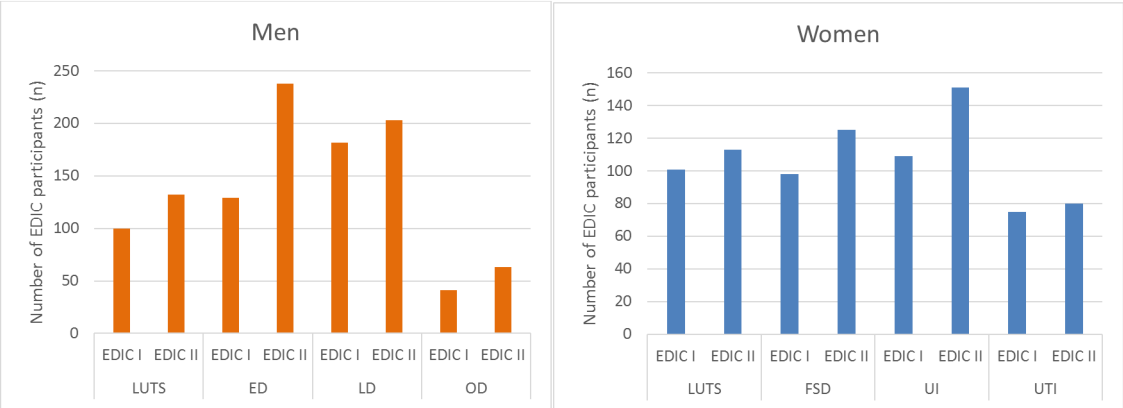

Figure 1a and 1b. Increased Prevalence of Urologic complications in men (a) and women (b) from Uro EDIC year I and II.

Data from Wessels, H. et al., 2018, Diabetes Care

Increased prevalence of urologic complications from EDIC I to EDIC II in men and women.

Cohort totals: Women n=508, Men n=551

*EDIC: Epidemiology of Diabetes Interventions and Complications study

*LUTS: Lower Urinary Tract Symptoms

*FSD: Female Sexual Dysfunction

*UI: Urinary Incontinence

*UTI: Urinary Tract Infection

*ED: Erectile Dysfunction

*LD: Low Desire

*OD: Orgasmic Dysfunction

Table 1.

Studies of bladder dysfunction in diabetes

Authors (Year)	Overall Population (Diabetes type)	Definition of Neuropathy	Definition of Bladder Dysfunction	Findings
Men and Women				
Wessells et al (2018)	1059 T1DM DCCT/ EDIC study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	LUTS, UTI	In men, age associated with LUTS, and persistence of LUTS. HbA1C in women associated with emergence of LUTS and persistent UI.
Wilke et al (2015)	456,586 T2DM	n/a	UTI	Highest UTI event rates in those aged >89 years. Most important factors in UTI risk were older age, female gender, UTIs in the previous 2 years, number of comorbidities, and at
Pavy-Le Traon et al (2010)	684 T1DM	CAN severity Ewing Score (0-5): deep breathing, Valsalva, stand test, HRV, SBS	Bladder dysfunction symptoms	Bladder dysfunction independently associated with CAN
Liu et al (2011)	1359 T2DM	Detailed interview	OAB symptom score	The prevalence of OAB and OAB wet was 2.4-fold and 4.2-fold greater, in patients with diabetes duration>10 years and age>50 years. Age and male sex were independent risk factors for OAB, age and waist circumference were independent risk factors for OAB wet.
Esteghamati et al. (2007)	66	Neurological consultation for the presence of peripheral somatic neuropathy (sensory, motor).	IPSS	Female sex was associated with increased bladder capacity. Male sex was associated with decreased bladder compliance and bladder outlet obstruction. Old age associated with low flow rate and outlet obstruction. Detrusor instability associated with shorter duration of diabetes. Peripheral somatic neuripathy associated with low flow rate.
Kebapci et al (2007)	54 T2DM 27 males 27 females	CAN: deep breathing, Valsalva, stand test	LUTS: IPSS, Urinary Incontinence, Urodynamic studies	QT prolongation associated with with increased Post void residual urine OR 2.33 (0.16-34.89)
Low et al (2004)	231 T1DM/T2DM	Autonomic Symptom Profile (ASP) Composite Autonomic Severity Score (CASS)	ASP urinary domain: Bladder Dysfunction, Sexual dysfunction (males only)	Significant correlations between ASP urinary domain and overall CASS and domain scores
Ueda et al (2000)	3500 n/a	23 item urinary incontinence questionnaire	Urinary incontinence	Women with history of diabetes mellitus had increased risk for UI
Ueda et al (1997)	63 Diabetes *	Sympathetic skin response: Mystro plus MS20	Volume at first desire to void Max bladder capacity Bladder pressure Residual urine	Mean Vol. at first desire to void, Max bladder capacity lower for Sympathetic Skin response absent. Mean Bladder pressure and Residual urine greater for Sympathetic Skin response absent.
Men				
Pop-Busui et al (2015)	635 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	LUTS: AUASI 8-35	LUTS prevalence: 158 (25%) Odds of ED+LUTS: 2.65 (1.47-4.79)
Sarma et al (2012)	186	n/a	LUTS: AUASI	Men with diabetes had higher odds of moderate/severe LUTS. Those not taking medications had higher odds of worse LUTS than those taking medications.

Authors (Year)	Overall Population (Diabetes type)	Definition of Neuropathy	Definition of Bladder Dysfunction	Findings
Bansal et al (2011)	52 Diabetes *	Sympathetic skin response: Medtronic electromyographic system	LUTS: IPSS 8-35 Urodynamic studies	Diabetic cystopathy correlated with abnormal motor and sensory nerve conduction velocity studies and abnormal sympathetic skin responses
Joseph et al (2003)	708 n/a	n/a	LUTS: AUASI	History of diabetes was positively associated with LUTS
Michel et al (2000)	1290 Diabetes *	n/a	LUTS: IPSS	Older age and IPSS independently associated with increased odds of having diabetes. Diabetics had significantly greater IPSS and smaller maximum flow rate than non-diabetic patients.
Women				
Tai et al. (2016)	400 T2DM	Medical history of peripheral neuropathy	LUTS: AUASI	Women with poor glycemic control more likely to develop urinary retention. Diabetic neuropathy significant predicted LUTS.
Hotaling et al (2016)	571 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	UI: Sandvik Severity Index 3-12	UI prevalence: 172 (30%)
Lenherr et al (2016)	64 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	UI: Sandvik Severity index	15.3% of women with T1DM reported incident UI. Mean HbA1c was associated with increased odds of incident UI.
Lenherr et al (2016)	572 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	Self-report	15% of women reported at least one UTI in 12 months. Higher HbA1C associated with number of UTIs.
Boyko et al (2005)	218 Diabetes *	n/a	UTI, asymptomatic bacteriuria, PVR	Increased risk of UTI in women with diabetes, specifically women taking insulin and women with longer diabetes duration. Increased asymptomatic bacteriuria in women with diabetes.
Lee et al (2004)	194	Detailed questioning about symptoms of paresthesia, dulled sensation, pain in legs and feet, measurement of sensory threshold (vibratory and thermal) on the feet.	LUTS: AUASI, PVR	Women with diabetes had higher nocturia scores, weaker urinary streams, less voided volumes, and lower maximal flow rates. Diabetes significant associated with decrease in baseline maximum flow. Peripheral neuropathy indepently associated with decrease in emptying efficiency.
Geerlings et al (2000)	589 T1DM and T2DM	n/a	UTI	14% of women with T1DM developed UTI, 23% of women with T2DM developed UTI. Risk factors for UTI development was presence of asymptomatic bacteriuria

* Type of diabetes not indicated

Note: AUASI, American Urological Association Symptom Index; CAN, cardiovascular autonomic neuropathy; DBP, diastolic blood pressure; DCCT/EDIC, Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications; ED, erectile dysfunction; HRV, heart rate variability; IIEF, International Index of Erectile Dysfunction; IPPS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; SBS, spontaneous baroreflex slope; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; OAB, overactive bladder; UI, urinary incontinence

Table 2.

Studies of sexual dysfunction in diabetes

Authors (Year)	Population	Definition of Autonomic Neuropathy	Definition of Sexual Dysfunction	Findings
Men and Women				
Wessells et al. (2018)	1059 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	ED: IIEF single item FSD: FSFI-R	Majority with complication at UroEDIC I had persistence of the complication at UroEDIC II. In men, age associated with persistence of ED, OD, and LD. HbA1C associated with persistence of OD and ED. In women, age associated with with emergence of FSD, persistence of FSD. HbA1C in women associated with emergence of LUTS and persistent UI
Bak et al. (2017)	215 T2DM	Medical history	ED: IIEF FSD: FSFI	Sexual dysfunction correlated with age and duration of diabetes. Sexual disorders correlated with occurrence of depression and acceptance of illness.
Bjerggaard et al. (2015)	1170 T2DM	n/a	ED: IIEF FSD: FSFI-R	54% of men and 12% of women had sexual dysfunction
Pavy-Le Traon et al. (2010)	684 T1DM	CAN severity Ewing Score (0-5): deep breathing, Valsalva, stand test, HRV, SBS	Erectile dysfunction symptoms (erection frequency and maintenance)	Erectile dysfunction independently associated with CAN severity (p=0.0005)
Low et al. (2004)	231 T1DM/T2DM	Autonomic Symptom Profile (ASP) Composite Autonomic Severity Score (CASS)	ASP: Sexual dysfunction	Men with T1DM and T2DM had significantly worse sexual function scores compared to controls (p<0.05 for both)
Men				
Corona et al. (2016)	449 T2DM	Medical interviews	ED: IIEF	The combination of phosphodiesterase 5 inhibitor therapy and an integrated approach to achieving metabolic targets in men with T2DM can improve sexual function and depressive symptoms.
Ghafoor et al. (2015)	200 Diabetes patients with ED *	Composite Autonomic Severity Score (CASS)	ED: IIEF	Autonomic Neuropathy prevalence: 86 (43%)
Pop-Busui et al. (2015)	635 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	ED: IIEF single item	ED prevalence: 290 (46%) Odds of ED+LUTS: 2.65 (1.47-4.79)
Bansal et al (2011)	52 Diabetes *	Sympathetic skin response: Medtronic electromyographic system	ED: 5-item score <21	Diabetic neuropathy not associated with ED
Penson et al. (2009)	713 T1DM	IIEF	ED, OD, DL	ED was present in 34%, OD in 20%, and DL in 55%. All cause bother, though ED causes more general sexual bother.
Hamdan et al. (2008)	56 T2DM, 30 controls	R-R variation <10, Valsalva ratio ≤1.2	Ultrasound penile vasculature assessment PSV≤30 cm/sec and EDV≥5 cm/sec	Diabetic ED group had higher HbA1c and oxidative stress levels (p=0.001), lower R-R ratio (p<0.002) and neurophysiological parameters compared to controls
Debono et al. (2008)	22 T2DM	CAN: Age specific Inspiration Ratio (E/I from R-R variation), Valsalva ratio ≤1.2, standing 30:15 ratio ≤1.031	ED: IIEF≤21	No significant associations observed between CAN measures and ED

Authors (Year)	Population	Definition of Autonomic Neuropathy	Definition of Sexual Dysfunction	Findings
Burke et al. (2007)	53 Diabetes *	n/a	Previously validated Male sexual function index	Men with diabetes at baseline has greater dysfunction in all 5 sexual domains (sexual drive, erectile function, ejaculatory function, sexual problem assessment, and sexual satisfaction).
Pegge et al. (2006)	33 ED (20 T1DM/ T2DM), 30 controls (15 T1DM/T2DM)	Inspiration Ratio (E/I from R-R variation), Valsalva ratio	ED: IIEF	E/I ratios of diabetic men significantly lower than controls ($p<0.02$). No difference in CAN measures by ED status.
Bleustein et al. (2002)	73 (53 ED, 20 No ED)	Index finger and glans penis vibration, pressure, spatial perception, warm/cold thermal thresholds	ED: IIEF≤25	Neuropathic measures of the glans penis significantly associated with ED
De Angelis et al. (2001)	60 T2DM	CAN: Deep breathing, Squatting vagal test, Squatting sympathetic test, Heat-pain threshold, Warm threshold, Vibratory threshold	ED: IIEF≤25	Heat-pain, warm perception thresholds, cardiovascular reflex tests abnormal in men with ED ($p<0.05$)
Sairam et al. (2001)	129 n/a	n/a	ED: men were already diagnosed	The prevalence of undiagnosed DM was higher in men with ED than in the general population.
Hecht et al. (2001)	49 ED	15-item Autonomic Symptom questionnaire, Nerve Condition studies, Sphincter ani electromyography, Vibratory thresholds, Temperature Perception thresholds, CAN: Heart rate variability	ED: physician referral based on diagnosis	Frequency of abnormal nerve conduction studies, heart rate variability higher in men with diabetic ED
Fedele et al. (2001)	1010 T1DM/T2DM	Ewing Score ≥2 positive responses	ED: failure to achieve and maintain erection sufficient for satisfactory sexual performance	Erectile dysfunction associated with autonomic neuropathy (RR=1.16)
Wellmer et al. (1999)	79 T1DM/T2DM	Thermal thresholds, Vibration thresholds, Light touch thresholds, Axon reflex vasodilation, Axon reflec sweating, Sural and peroneal nerve conduction studies	ED: erection insufficient for intercourse and erection could not be sustained for duration of intercourse	Neuropathic pain ($p<0.05$), abnormal sensory axon-reflex vasodilation ($p<0.001$), and decreased sural nerve action potential ($p<0.01$) significantly greater in men with ED
Women				
Hotaling et al. (2016)	371 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	FSD: FSFI-R	FSD prevalence: 153 (41%)
Maiorino et al. (2016)	145	Diabetic neuropathy index	FSD: FSFI Sexual activity-related distress: FSDS	Depression and mental health were independent predictors of FSD. Sexual function was significant impaired in women on multiple daily injection.
Elyasi et al. (2015)	150	Medical record history	FSD: FSFI	High prevalence of sexual dysfunction (79%), especially among those with depression.
Enzlin et al. (2009)	424 T1DM DCCT/ EDIC Study	CAN: R-R variation <15, or R-R variation 15-19.9 plus Valsalva ratio ≤1.5, 10 mm Hg drop in DBP	FSD: FSFI-R	35% of women had FSD. Depression and marital status were significant predictors of FSD.

Authors (Year)	Population	Definition of Autonomic Neuropathy	Definition of Sexual Dysfunction	Findings
Fatemi et al. (2009)	50 T2DM	n/a	FSD: Arizona Sexual Experience Scale (ASEX) form	Diabetes significantly impaired the sexual performance of diabetic women. Determinants of sexual function included age and duration of diabetes
Abu Ali et al. (2008)	1137	Medical record history of autonomic neuropathy	FSD: FSFI	No independent association between autonomic neuropathy and FSD

* Type of diabetes not indicated

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Table 3.

Women with autonomic neuropathy have higher odds of FSD and UTI; Men with autonomic neuropathy have higher odds of LUTS, ED and OD.

Women				
	LUTS	**FSD**	**UI**	**UTI**
N total respondents	579	371	571	555
N (%)	128 (22)	153 (41)	172 (30)	95 (17)
Autonomic Neuropathy	1.28 (0.85-1.92)	**1.67 (1.07-2.60)**	1.28 (0.88-1.85)	**1.57 (1.00-2.47)**
Men				
	LUTS	**ED**	**LD**	**OD**
N total respondents	643	635	598	564
N(%)	158 (25)	290 (46)	243 (41)	83 (15)
Autonomic Neuropathy	**2.07 (1.42-3.01)**	**2.82 (2.01-3.94)**	1.28 (0.91-1.80)	**2.40 (1.49-3.88)**

Data from Wessels, H. et al., 2018, Diabetes Care

Note: Data are odds ratios (95% CI) unless otherwise specified. Significant values are in boldface type. Autonomic neuropathy defined at EDIC year 16/17 as an R-R variation <15 or R-R variation <20 in combination with a Valsalva ratio ≤1.5 or a decrease of >10 mmHg in diastolic blood pressure upon standing. DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; LUTS, lower Urinary tract symptoms; UI, urinary incontinence; UTI urinary tract infection; ED, erectile dysfunction; OD, orgasmic dysfunction; LD, low sexual desire; FSD, female sexual dysfunction