

SIGNIFICANCE

Burden and impact of bladder dysfunction in diabetes. The incidence of type 1 diabetes (T1D) has been steadily rising among children and young adults in the U.S. and worldwide.^{1,2} T1DM is typically diagnosed at the beginning of the life span, making diabetic complications in this population particularly challenging as they appear at relatively young ages. Paradoxically, improved treatments for T1D that extend longevity also impact prevalence and incidence of vascular and neuropathic complications. In turn, these complications, including urological complications such as bladder dysfunction, have a profound impact on patients' quality of life (QOL). Not only do urological problems drive care-seeking behavior and per capita cost,^{3,4} costs of care are higher in T1D^{5,6} as these complications develop at earlier ages and are more likely to be treatment-refractory.⁷ It is therefore not surprising that Healthy People 2020 identified bladder dysfunction as an emerging issue for persons with diabetes.⁸ However, our team does not believe that urologic complications of diabetes are an emerging problem; we believe these complications result from longstanding elevated blood glucose, are highly prevalent in both men and women, and that there is sufficient groundwork in this area to implement strategies identifying promising directions for therapeutic exploration. Over the past 17 years, our multidisciplinary research team has leveraged the resources and infrastructure of a well-described cohort of diabetic participants to provide an exhaustive description of urinary symptoms and sexual dysfunction in people with T1D. **At this point in our research program, we are conservatively, but decidedly, moving to integrate a systems biology approach into our effort to identify and characterize the subset of T1D participants with the most severe bladder dysfunction. Using genomic tools to identify potential transcriptional profiles that explain variation in the severity and persistence of bladder function and symptoms in these participants are necessary first steps to begin identifying potential biomarkers and therapeutic targets for future drug development.**

Current understanding of bladder dysfunction in diabetes. Although lower urinary tract dysfunction is common in men and women with diabetes, there is a lack of clarity, understanding, and standardization of nomenclature around diabetic bladder dysfunction.⁹ Diabetic cystopathy (DC) has been classically described as diminished bladder sensation, poor contractility, and increased post-void residual urine.¹⁰ Prevalence estimates range from 25%-90%,¹¹ reflecting a lack of standardized diagnostic criteria and differences in populations from which these estimates are derived. Cases of severe underactive, flaccid, hypotonic or atonic bladder are an uncommon end organ result of diabetes; nevertheless, among affected individuals, DC has a major impact on QOL.¹² Current understanding of diabetic bladder dysfunction indicates a progressive condition involving multiple aspects of lower urinary tract dysfunction. This dysfunction initially manifests as polyuria driven by hyperglycemia, progresses to urothelium-, nerve- and muscle-related abnormalities, ultimately leading to overactive bladder (OAB) characterized by urinary urgency, frequency, nocturia and urge UI.^{11,13-20} (Figure 1). If left untreated, DC, characterized above as diminished sensation and urine retention, may appear and progress to bladder failure. It is unknown whether this spectrum represents a linear progression²¹ or distinctive endotypes²² with different pathophysiologic mechanisms. Endstage DC has long been associated with autonomic neuropathy.

However, a growing body of research in animal models reviewed by Birder²³ and Dalghi²⁴ implicates alterations in urothelial mechanosensing and signal transmission to afferent neurons in the pathophysiology of detrusor overactivity and urinary incontinence.²⁵⁻

UroEDIC Bladder will significantly enhance our understanding of diabetic bladder dysfunction in T1D by integrating multiple levels of data including autonomic and urothelial measures, and extending our prior work to determine who is at highest risk for severe and persistent symptoms by using a systems biology approach to generate novel models of bladder function and failure in T1D.

Figure 1. Phenotypes of Lower Urinary Tract in Early and Late Phases of Diabetic Bladder Dysfunction

