



# The Impact of Diabetes on the Lower Urinary Tract Dysfunction

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Diabetes mellitus has reached epidemic proportion in Asia. The researches of lower urinary tract dysfunction in diabetes have received close attention in the last years. For decades, the main focus of diabetes associated lower urinary dysfunctions has been referred to diabetic cystopathy. In a traditional viewpoint, the voiding dysfunction of diabetes is attributed to the impairments of vesical afferents and efferents pathway. In fact, diabetes can affect the lower urinary tract function via the mechanisms of osmolarity diuresis, metabolic perturbation, microvascular damage and urothelial dysfunction in diabetes. The interaction of benign prostatic hyperplasia, metabolic syndrome and obesity on diabetic lower urinary tract dysfunction is another interesting issue for scientists. In this review, current knowledge about the pathophysiology and clinical presentations of lower urinary tract dysfunction in diabetes is discussed. Therefore, we could get forward to future research. (JTUA 20:155-61,2009)

*Key words:* diabetes, bladder, urination disorders, neuropathies.

## INTRODUCTION

During recent decades, rapid economic development and urbanization have increased the prevalence of type 2 diabetes in Asia.<sup>1</sup> Lower urinary tract dysfunctions secondary to type 2 diabetes are common, chronic and costly disorders. They impose an important threat on the lower urinary tract morbidity and economic burdens for our future generations.

The main focus of diabetes associated lower urinary tract dysfunctions has been referred to diabetic cystopathy for many years. Prevalence estimates of urodynamically diagnosed bladder cystopathy have ranged from 25% to 90%.<sup>2</sup> The wide variation in estimates reflects the lack of validated or standardized clinically significant measures used to diagnose bladder cystopathy as well as the selected referral based populations that have often been studied.

The prevalence of unrecognized diabetic bladder dysfunction among diabetic women in clinical settings has reached to 22%.<sup>3</sup> The prevalence of diabetic bladder dysfunction is not related the sex and age of the patients, but increased with the duration of diabetes mellitus.<sup>4</sup> Although the prevalence of diabetic bladder dysfunction increased with the duration of diabetes, diabetic bladder dysfunction can also occur silently and early in the course of diabetes.<sup>5</sup> One reasonable explanation for the early presentation of diabetic bladder dysfunction is that diabetic patients are hyperglycemic for up to 6 years before being diagnosed.

Although lower urinary tract dysfunction is a common health problem in patients with diabetes, there is a lack of clarity and understanding of pathophysiology in this issue. Recent evidences have showed that the impact of diabetes on the lower urinary tract is multifactorial.<sup>6</sup> Osmolarity diuresis effect, metabolic perturbation, microvascular damage and neuropathy of diabetes may cause dysfunctions of smooth muscle, urothelium and neuronal components in the bladder. Development of lower urinary tract symptoms, urinary incontinence, detrusor underactivity or detrusor overactivity could be found in the progression of diabe-

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tes among patients. Symptomatic urinary tract infections or asymptomatic bacteriuria is considered as a complication of diabetes among diabetic women.<sup>6-8</sup>

Although the diagnosis of diabetic bladder dysfunction can be made by the urodynamic studies, the effect of current treatment is still limited. Further studies of formulating suitable therapies for diabetic bladder dysfunction are needed.

### **PATHOGENETIC MECHANISMS OF DIABETES-ASSOCIATED LOWER URINARY TRACT DYSFUNCTION**

The pathophysiology of diabetes-associated lower urinary tract complications is various and unclear. Recently, more evidence suggests that diabetes can affect the lower urinary tract function by multifactorial pathogenetic mechanisms.<sup>6</sup> The diabetic bladder dysfunction can be a result of an alteration in the physiology of the detrusor muscle cell, the function of the neuronal component, or urothelial dysfunction. In addition, diabetes can cause the lower urinary tract dysfunction through the interaction with benign prostate hyperplasia, obesity, and metabolic perturbations. These changes could explain the varied clinical presentations in diabetic patients.

#### **The co-morbidity of diabetes and benign prostate hyperplasia**

Benign prostatic hyperplasia (BPH) is the most common non-malignant condition of the prostate in aging men, characterized by abnormal cell proliferation. Diabetes is suggested to be a risk factor for the development and progression of BPH.<sup>9,10</sup> Increased sympathetic nerve activity is common in either BPH or diabetic patients. The BPH patients with diabetes suffered more severe lower urinary tract symptoms than those without diabetes.<sup>9</sup>

Diabetic vascular damage and atherosclerosis could cause hypoxia in transitional zone of the prostate. They were proposed to be the pathogenesis of BPH.<sup>10</sup> Moreover, the insulin-like growth factors axis has been implicated in prostate cancer and BPH. The high insulin-like growth factors-I and low insulin-like growth factors binding protein-3 were reported to be associated with the growth of the prostate.<sup>11</sup> However, a recent large-scale community base study showed the presence of diabetes may be less related to prostate growth and more related to the dynamic components of lower urinary tract function.<sup>12</sup>

Either storage or empty symptoms were increased

in the BPH patients with diabetes.<sup>9</sup> Empty symptoms including straining, intermittency, terminal dribbling and weak stream may signify bladder outlet obstruction from BPH. However, similar symptoms may also result from bladder dysfunction due to microvascular complication and denervation among men with diabetes. The diabetic patients combining with BPH will accelerate the lower urinary tract dysfunction. To treat the voiding dysfunction of diabetic patients with BPH by using  $\alpha$  blockers or prostatectomy might benefit the patients from deterioration of bladder function.<sup>13,14</sup>

#### **The effects of diabetes on afferent and efferent pathways of the bladder**

In a traditional viewpoint, the impairment of A $\delta$  fiber in bladder afferents is responsible for the development of diabetic bladder dysfunction. Activation of the intramural afferent A $\delta$  fiber by the filling-induced stretch of detrusor muscle is the most important sensory function to evoke a micturition in human. The decreased sensation of bladder filling caused unresponsive in bladder wall stretch and the bladder overdistention. Repeated bladder overdistentions cause the hypocontractility of the diabetic bladder.

Recently, the theory that bladder overdistention causes the diabetic bladder dysfunction has been challenged.<sup>6,15</sup> In the streptozotocin induced diabetic model, deficiency of axonal transport of nerve growth factor in the bladder afferent pathway could attenuate the detrusor contractility directly.<sup>16</sup> Furthermore, nerve growth factor supplement gene therapy has proved to restore decreased nerve growth factor expression in the A $\delta$ -fiber afferent pathways of the bladder, thereby improving hypoactive bladder function and increased bladder voiding efficiency in diabetes.<sup>17</sup> In observing diabetic women with unrecognized diabetic bladder dysfunction, there are few patients with a large bladder capacity.<sup>15</sup> Hence, the overdistention of the bladder is not a dominant mechanism in the incipient stage of diabetic bladder dysfunction.

The role of vesical C-fiber neuropathy in the development of diabetic bladder dysfunction is another interesting issue. C-fiber neuropathy is common in diabetic peripheral neuropathy. Diabetes can also affect C-fiber afferent pathways of the bladder. Activation of suburothelial C-fiber afferent nerve of the bladder involves in the initiation of micturition and this mechanism is dominant in some pathological status. Scientists tried to validate the correlation of bladder C-fiber neuropathy, but lacked of direct evidence to show the association between C-fiber neuropathy and diabetic bladder

dysfunction.<sup>18-20</sup> Conventional urodynamic studies and ice water test can not provide a good sensitivity to validate this hypothesis.<sup>18,19</sup> Recently, we applied the intravesical current perception threshold test to record the response of A $\delta$ - and C- fibers of the bladder in diabetic women.<sup>21</sup> This study showed an association between the uroflowmetry parameters and the vesical A $\delta$  and C fiber neuropathy in the diabetic women with detrusor underactivity. These data suggested that A $\delta$  and C fiber bladder afferent pathways be damaged and resulting in early diabetic bladder dysfunction. In addition, an increased threshold of C fiber afferent pathway in diabetic patients with detrusor underactivity is a probable cause of insensitivity to inflammations occurring in the bladder of diabetic patients when asymptomatic bacteriuria occurs.

The impairments of efferent pathways of the bladder in diabetic patients are considered causing the detrusor overactivity with impaired contractility. Diabetes can cause demyelination and axonal degeneration of the bladder efferents and result in a decreased acetylcholinesterase activity in diabetic patients.<sup>22</sup> Partial autonomic denervation induced an up-regulation of M2 receptors and decreased cholinergic transmission.<sup>23</sup> Increased M2 receptors inhibit bladder relaxation and cause an overactive bladder and detrusor overactivity. In a type 2 diabetic GK rat model,<sup>24</sup> the decreased cholinergic transmission and unchanged responsiveness of detrusor contractility to adenosine triphosphate and KCl were noted in the bladder smooth muscle bath experiment.

Central nerve system dysfunction may interfere with diabetic bladder dysfunction in conjunction with peripheral neuropathy.<sup>25</sup> Detrusor overactivity is related to diabetic bladder dysfunction due to a high prevalence of stroke in diabetic patients.<sup>20</sup> The major presentation of voiding dysfunction in patients with stroke is detrusor overactivity with impaired contractility. Additionally, there are possible lesions within spinal cord that could interfere to diabetic bladder dysfunction. An electrophysiological study by measuring somatosensory evoked potentials in patients with diabetic bladder dysfunction showed delayed central sensory and motor time in the test.<sup>25</sup> This study suggests the contribution of spinal cord dysfunction in diabetic bladder dysfunction.

### ■ Urothelium dysfunction in diabetes

The urothelium can function as a sensor to control the bladder function and dysfunction. It has been reported that M2 and M3 muscarinic receptors increases in the urothelium of the streptozotocin induced diabetic rats.<sup>23,26</sup> The increased M2 and M3 receptors in the

urothelium can increase sensory nerve activity to facilitate the detrusor contraction. In addition, the bradykinin-evoked tonic contractions were reduced significantly by removing the urothelium in the streptozotocin induced diabetic rats.<sup>27</sup> Bradykinin and adenosine triphosphate can significantly increase the endogenous release of prostaglandins from urothelium.<sup>28</sup> The prostaglandins can sensitize sensory nerves and increase the sensitivity of detrusor muscle to stimuli. The increased activity of M2, M3 and bradykinin receptors were proposed to be pathogeneses of detrusor overactivity in diabetes.

### ■ Bladder smooth muscle dysfunction in diabetes

Diabetes has been shown to induce alteration in bladder tissue composition and compliance. In streptozotocin induced diabetic rats, detrusor hypertrophy can be induced by the diuresis effect of hyperglycemia in the early stage of diabetes.<sup>29</sup> Then, the diabetes-specific changes in the mechanical properties of bladder wall occur later. Bladder tissue remodeling were also associated with down regulation of TGF- $\beta$ 1 and collagen mRNA levels, and the increase of elastin synthesis.<sup>30</sup> Therefore, increases in compliance of the bladders in diabetes result not only from diuresis-driven reduction of collagen synthesis but also from the increased elastin synthesis. In addition, oxidative stress was reported to involve in the detrusor dysfunction. Hyperglycemia induces production of oxygen radicals, which can cause oxidative damage to detrusor muscle and impairment to vascular endothelium in the lower urinary tract.<sup>31</sup> Evaluating by electron microscopy, the swelling of mitochondria in bladder smooth muscle indicated that accumulation of free radicals may be a cause of detrusor dysfunction in the streptozotocin induced diabetic rats.<sup>32</sup> Moreover, an increase in lipid peroxides and sorbitol are associated with a decrease in detrusor muscle force in the alloxan induced diabetic rabbit model.<sup>33</sup>

### ■ Urethral dysfunction in diabetes

Endothelial dysfunction and nitric oxide (NO) deficiency are the important pathogeneses in the development of diabetes complications. An important action of NO on the outflow region including urethra, trigone and prostate appears to be widely accepted.<sup>34</sup> In the streptozotocin induced diabetic rats, smooth and striated muscle dysfunction of urethral outlet can be treated by terazosin and L-arginine therapy.<sup>35,36</sup> The major component of diabetic urethropathy is unrelaxation of urethra.<sup>37</sup> Unlike bladder afferent neuron, diabetic neuropathic alteration in urethral afferent neurons is hyperexcitable in the pro-

gression of diabetes.<sup>38</sup> The atrophy of muscle in external urethral sphincter was reported and attributed to the hyperglycemic effect of diabetes.<sup>39</sup> Hence, the  $\alpha$ -blocker may play a role in the treatment of diabetic lower urinary tract dysfunction.<sup>35</sup>

### ■ **The effect of obesity and metabolic syndrome on lower urinary tract dysfunction in diabetic patients**

Currently, metabolic syndrome is considered as an independent risk factor of bladder dysfunction. Lower urinary tract symptoms were strongly positive association with metabolic syndrome with or without diabetes.<sup>40</sup> Men with metabolic syndrome have an increase of odds in nocturia, incomplete bladder emptying, weak stream and hesitancy. Metabolic syndrome is reported to be a prediabetic status. Obesity and insulin resistance as well as other factors such as aging, proinflammatory state and hormonal changes, have been suggested as the cause of metabolic syndrome.

Obesity and male gender have been reported to be associated with metabolic syndrome and precipitate the bladder dysfunction.<sup>41-43</sup> The estrogen can improve insulin sensitivity in fructose-fed rats.<sup>42</sup> Obesity alone or combining with diabetes can precipitate the lower urinary tract dysfunction such as overactive bladder and stress urinary incontinence in women.<sup>41</sup> High body mass index directly related to the development of type 2 diabetes and also increases intra-abdominal pressure, leading to urinary incontinence. Hyperlipidemia is also an independent factor for overactive bladder.<sup>44</sup> In a long-term fructose fed rat model, researchers reported that proinflammation and myopathy of the bladder induced by metabolic perturbation are the causes of metabolic bladder dysfunction.<sup>45</sup> The main presentation of metabolic bladder dysfunction is detrusor overactivity with impaired contractility. A lot of diabetic patients with bladder dysfunction have suffered from metabolic perturbations. Hence, we support the role for metabolic perturbations in the etiology of bladder dysfunction in diabetes.<sup>45</sup>

## **CLINICAL PRESENTATIONS OF LOWER URINARY TRACT DYSFUNCTION IN DIABETES**

Current understanding of diabetic bladder dysfunction reflects a progressive condition encompassing a broad spectrum of lower urinary tract symptoms.<sup>2</sup> Based on disease progression and urodynamic findings, the diabetic bladder dysfunction can be stratified into compensated and decompensated stages.<sup>21</sup> The key feature

of the decompensated diabetic bladder dysfunction is different from the compensated diabetic bladder dysfunction in urinary retention. The compensated stage has been named incipient stage, incipient asymptomatic stage or the early stage. The incipient stage means the diabetic patients in this stage may or may not have lower urinary tract symptoms as well as lacking of self-perception. In contrast, the decompensated stage of diabetic bladder dysfunction is the end-stage of diabetic cystopathy. The decompensated stage of diabetic bladder dysfunction is notorious for sudden onset of urinary retention by overdistention of the bladder, secondary urinary tract infections and renal function deterioration. The decompensated stage of diabetic bladder dysfunction is also named classic diabetic cystopathy, the advanced stage of diabetic bladder dysfunction and the late stage of diabetic bladder dysfunction. Diabetic patients in this advanced stage must be received catheterization, Crede maneuver or parasympathetic drugs, otherwise severe complications occurred.

### ■ **The development of lower urinary tract symptoms in type 2 diabetic patients**

The patients with the early stage of diabetic bladder dysfunction may or may not have lower urinary tract symptoms. However, presentation of lower urinary tract symptoms is increased in diabetic women, particularly nocturia and weak stream.<sup>2</sup> Increased storage symptoms were also noted in men with diabetes.<sup>12</sup> Is the presence of lower urinary tract symptoms caused by the high prevalence of diabetic bladder dysfunction in diabetic patients or the diuretic effect of diabetes? Researchers reported that a high lower urinary tract symptoms score is a good marker of diabetic bladder dysfunction.<sup>15</sup>

### ■ **Overactive bladder in diabetic patients**

Recent evidence also showed that the increase risk of an overactive bladder in diabetic patients is related to the peripheral nerve irritation, increased bladder sensation and detrusor overactivity.<sup>20</sup> The presence of an overactive bladder in diabetic patients could be considered a sign of vesical neuropathy.<sup>15</sup> Decreased functional bladder capacity is one of the most important causative factors among diabetic patients with an overactive bladder. Either detrusor underactivity or detrusor overactivity could lead to a low functional capacity and induced overactive bladder in humans.<sup>21</sup>

### ■ Nocturia in diabetic patients

Nocturia is the commonest urinary symptom among diabetic patients.<sup>3,12</sup> Women with diabetes may have an increased risk of nocturia even without any bladder dysfunction.<sup>15</sup> Men with diabetes also have a double risk in nocturia.<sup>12</sup> Nocturia is a bothersome symptom that profoundly influences general health and quality of life. Nocturnal polyuria is the major cause of nocturia in diabetic patients. Osmolarity diuresis of diabetes, hypertension and old age are the potential causes of nocturia for type 2 diabetic patients.

### ■ Urinary incontinence in diabetic patients

There are several reports of urinary incontinence for diabetic women.<sup>46,47</sup> Urinary incontinence is highly prevalent among postmenopausal women. In developed countries, diabetes affects mainly those who are older than 65 years.<sup>1</sup> But in developing country the mean age of type 2 diabetic women are between 45 and 64 years. The postmenopausal effect must involve in the mechanism of urinary incontinence among diabetic women. Women with diabetes or impaired fasting glucose are more likely to experience severe urinary incontinence.<sup>47</sup> The risk factors of urinary incontinence in diabetic women are urinary tract infections history, combining with obesity.<sup>46</sup> In a long term study, urgent incontinence is more prominent in diabetic women after the adjustment of confounders.<sup>48</sup>

### ■ The presentations of urodynamic findings

Generally, type 2 diabetic patients evaluated with urodynamic studies are of advanced age and an overlap existed with other age-related urological diseases that have urodynamic consequences. Therefore, the diagnosis of diabetic bladder dysfunction is most readily made with urodynamic testing. There are conflicting data regarding urodynamic findings in patients with diabetes. Early studies suggested that urodynamic findings include impaired bladder sensation, increased cystometric capacity, decreased detrusor contractility and increased post-void residual urine volume.<sup>4</sup> However, Kaplan et al. reported that detrusor over activity was the most common urodynamic observation (48%) in diabetic patients with voiding dysfunction.<sup>49</sup> In contrast, Ueda et al. showed that patients with diabetes have urodynamic changes consistent with those described with classic diabetic cystopathy.<sup>50</sup> Although detrusor over activity was diagnosed in 25% of patients, detrusor overactivity was not found in patients without stroke. Hence, to investi-

gate the urodynamic characteristics of diabetic bladder dysfunction, scientists should exclude the confounders of voiding dysfunction.

Both central and peripheral mechanisms could be implicated in the etiology of detrusor overactivity in patients with diabetes.<sup>21</sup> Yamaguchi et al. demonstrated that the frequency of multiple infarcts in patients with detrusor overactivity was 76.5% by using cerebral magnetic resonance imaging among diabetic patients with bladder dysfunction.<sup>20</sup> The effect of aging process is one of reasons that the diabetic patients may have detrusor overactivity. As mentioned previously, peripheral mechanisms of detrusor overactivity are considering the varied range of pathology within the nervous system, urothelium and detrusor muscle in diabetes.

Recently, we reported that the early presentations of diabetic bladder dysfunction.<sup>21</sup> The detrusor underactivity (34.9%), detrusor overactivity (14.0%) and bladder outlet obstruction (12.8%) were observed in diabetic women. The high prevalence of bladder outlet obstruction in diabetic women may be contributed to unrelaxation of urethra in diabetes.

## CONCLUSIONS

The impact of diabetes on the lower urinary tract is multifactorial. Male gender, obesity, hyperlipidemia, hypertension, microvascular damage have proposed to involve in the pathogenesis. During decades, scientist explored a lot of pathogenic mechanisms of lower urinary tract dysfunction in diabetes. However, there is still lacking of effective screening and treatment strategy. New research initiatives are needed to further treatment of diabetic cystopathy. Life style modification such as weight loss and exercise can decrease the effect of metabolic syndrome and insulin resistance. Scheduled micturition and self clean intermittent catheterization can decrease the complication of chronic urinary retention. Nerve growth factor gene therapy is promising in future. But now, there is still a long way to go.

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