비뇨기계 자율신경병증의 치료

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Introduction

- Urologic complications have increasingly become a concern in those affected by DM
- Genitourinary problems are included among these complications, related to both neuropathy and vasculopathy
- More than a quarter of diabetic patients will develop costly and debilitating urological complications such as incontinence, infections, loss of sensation and retention of urine
Introduction

The most important clinical features relating to genitourinary involvement in patients with diabetes
- bladder dysfunction
- sexual dysfunction
  1) erectile dysfunction
  2) retrograde ejaculation
Normal bladder function

Normal bladder function: storage & emptying

CNS

Autonomic & somatic nerve

Lower urinary tract

Inferior mesenteric ganglion

Sympathetic

Trigone

Urethra

Parasympathetic

Pelvic nerves

Hypogastric nerves

Somatic

External urethral sphincter

Muscles of the pelvic floor

T10–L2

S2–S4

Abrams P, Wein AJ. The Overactive Bladder—A Widespread and Treatable Condition. 1998
Physiology of storage and emptying

**Storage phase**
- Hypogastric nerve
  - Contracts bladder outlet
  - Inhibits detrusor
- Pelvic nerve
- External sphincter

**Voiding phase**
- Hypogastric nerve
- Contracts detrusor
- Inhibits bladder outlet
- Pelvic nerve
- Internal sphincter

PAG (Periaqueductal Gray)
- Pontine micturition center
- Pontine storage center
Bladder dysfunction

• Three important aspects of the diabetic cystopathy that may overlap
  - alterations in detrusor smooth muscle cells
  - changes in the innervation or functioning of the neuronal component
  - urothelial dysfunction

• Prevalence: 32-45%

Yoshimura N et al, BJU Int 2005;96:733-8
Ueda R et al J Urol 1997;157:580-4
Effects of DM on detrusor smooth muscle function

Yoshimura N et al, BJU Int 2005;96:733-8
Reduced production of nerve growth factor (NGF)

Yoshimura N et al, BJU Int 2005;96:733-8
Urothelium has a role in pathogenesis of DM cystopathy
Urothelium has a neuron-like property

- Release of neurotransmitters

![Graph showing release of neurotransmitters with concentrations in nanomoles (µM). CAP: Capsaicin, CPZ: Capsazepine, NIC: Nicotine, C6: Hexamethonium.]

Cook and McCleskey, Nature, 2000;407:951
Clinical features of diabetic bladder dysfunction

- Classic description of neuropathy is principally sensory - characterized by diminished sensation, poor contractility and increased postvoid residual urine (PVR)
  - this clinical picture is not common, however, and probably represents the end-stage of bladder involvement

- Motor neuropathy
  - bladder instability or hypersensitivity represent the most frequent findings in patients with diabetes
Broad spectrum of lower urinary tract dysfunction

- Lower urinary tract symptom in 164 patients with DM

- Urodynamic study in 86 female patient with DM
  - Detrusor underactivity (34.9%), Detrusor overactivity (14%), bladder outlet obstruction (12.8%), Normal (38.4%)

Kim JC et al, Kor J Urol 2009;50(suppl):193
Bladder dysfunction has a different etiology in men and women

- In women,
  - urinary incontinence, a characteristic symptom of overactive bladder syndrome (OAB), is most common

- Increased risk factor
  - menopausal and postmenopausal women with DM
    - increased risk of 30-100%
  - obesity

Bladder dysfunction has a different etiology in men and women

• In men,
  - lower urinary tract symptoms (LUTS) include straining, intermittency, postvoid dribbling and weak stream, and signs of denervation and poor detrusor contractility
  - Detrusor overactivity secondary to microangiopathy, which can also cause symptoms such as urinary urgency, frequency and nocturia

Men with DM have an increased risk of developing LUTS, reported to be 25-100% higher than in the general male population.

DM may be associated with a higher risk of developing BPH, whereas other authors report the opposite.

Investigation and evaluation for bladder dysfunction

- Initial steps: collecting medical history and symptom information
- Questionnaires and voiding diary
- Urinalysis & urine culture
- Uroflowmetry and residual urine check

- Urodynamic study including pressure-flow study
  - if management is unsuccessful
  - where there is doubt about the diagnosis
  - if surgical intervention is contemplated
**IPSS & voiding diary**

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Treatment and management of bladder dysfunction

- Depends on the symptomatic complaints, their severity, degree of bother and impact on QoL

- Management goals
  - relief of symptoms
  - prevention and treatment of infections
  - continence
  - adequate bladder emptying

- As first step of treatment, noninvasive strategies may be employed to avoid or eliminate residual urine
In patients with decreased sensation and prolonged voiding interval

- Timed voiding on a consistent and regular schedule (every 2-4 hrs)
- Double-voiding technique
  - attempting to empty the bladder by staying on the toilet and trying to void more than once with each trip to the toilet

Improve bladder emptying, improve continence, and minimize risk of infection

In patients with decreased sensation and prolonged voiding interval

- Bladder expression
  - abdominal straining (Valsalva maneuver)
  - manual compression of the lower abdomen (Credè’s maneuver)

↓

can be useful in facilitating micturition in the absence of increased intravesical pressure, or vesicoureteral reflux
Impaired detrusor contractility & nocturnal polyuria

- Clean intermittent catheterization (CIC)
  - abolish residual urine
  - decrease risk of urinary tract infection with potential deterioration of renal function

- Nocturnal polyuria
  - confining most fluid intake to the morning or early afternoon
  - avoiding caffeinated beverages
  - voiding before going to bed
Pharmacologic treatment

• Impaired contractility
  - cholinergic drug (bethanechol): little effective

• Overactive bladder (OAB) symptom
  - anticholinergics
  - careful use in men with bladder outlet obstruction
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<td>Tolterodine, Trospium, Solifenacine, Fesoterodine</td>
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<tr>
<td>Drugs with mixed action</td>
<td>Oxybutynin, Propiverine</td>
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Patients do not seek medical attention

- 25-50% of diabetic patients did not complain of urinary tract symptom

- Due to minimal urinary tract symptoms in diabetic patients, these patients may not seek medical attention until later in the course of diabetes when the bladder function has decompensated with urinary retention and recurrent urinary tract infection
Many patients may delay seeking urological evaluation

- Up to one third have urodynamically abnormal bladder function

- Deficient bladder sensation is irreversible and long-term follow up is necessary

- Careful surveillance for voiding symptoms and screening for elevated residual urine may be useful to prevent long-term complications

Sasaki K et al, Urol Clin N Am 2003;30:1-12
Erectile dysfunction (ED)

• Definition
  - The inability of the male to attain and maintain erection of the penis to permit satisfactory sexual intercourse
Erectile dysfunction (ED)

Penile anatomy
Prevalence of erectile dysfunction (ED)

- Prevalence
  - overall prevalence: 13%
  - closely related to age
    - 2% in young men (18-39 years)
    - 48% above 70 years
    - 5-15% in relation to age (40-70 years)

Feldman HA et al, J Urol, 1994;151:54-61
Several factors other than age significantly increase the risk of ED

- DM: most important risk factor for ED, with an odds ratio (OR) of 3

- Smoking: doubles the risk of developing ED
- Smoking + DM: five-fold
- DM + cardiopathy: eight-fold
- DM + cardiopathy + smoking: 12-fold

- Mean prevalence of ED is reported by many authors to be three times higher in men with DM than in the general population (range 30-40 %)

Risk factors for erectile dysfunction in men with diabetes

- Age (>50 years)
- Smoking
- Younger age at diagnosis
- Poor glycemic control
- Administration of certain drugs (antihypertensives, hormones)
- Presence of late complications (neuropathy and vasculopathy)

- Related to age, glycemic control, and duration of diabetes

Erectile dysfunction in relation to treatment of diabetes

- Related to some late complications associated with diabetes, such as autonomic and somatic neuropathy, and vasculopathy

<table>
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<td>Insulin</td>
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<td>Oral hypoglycemic agents and insulin</td>
<td>4.14 (3.42–5.02)</td>
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OR, odds ratio.
Pathogenesis of erectile dysfunction

- Neurogenic mechanisms
- Increased formation of advanced glycated endproducts (AGE)
- Endothelial damage resulting from impaired nitric oxide (NO) production

Ignarro LJ et al, J Pharmacol Exp Ther 1981;218:739-49
Evaluation of erectile dysfunction

- Diagnostic work-up of men with diabetes and ED should include a detailed history and a complete physical examination with measurement of testosterone levels.

- Evaluation using the IIEF-5 questionnaire.

- Heart function should be evaluated before starting any treatment.

International Index of Erectile Function (IIEF-5)

다음 각 질문을 읽고 대답하는 것을 주의하십시오.

1. 지난 6개월 동안 성생활을 하셨나요?
   1) 매주
   2) 남나
   3) 그래
   4) 두배
   5) 매우 놀라

2. 지난 6개월 동안 성생활으로 만족되었을 때 성교의 기대할 만큼 충분한 만족도는 어느 정도로 생각하시나?
   0) 성형혈관 없었다.
   1) 거의 만족도 또는 만족도 있었다.
   2) 가끔씩 (총 청주의 30%에서 전천히 이루어진)
   3) 중점적으로 (총 청주의 50% 정도)
   4) 대부분 (총 청주의 50% 이상의 원활한 성교의)
   5) 항상 또는 거의 항상

3. 지난 6개월 동안 성생활 중에 언제나 성기의 길이가 충분히 기적적적이었나?
   0) 항상
   1) 거의 안되다
   2) 가끔 (총 청주의 50%에서 전천히 이루어진)
   3) 대단히 (총 청주의 50% 정도)
   4) 대부분 (총 청주의 50% 이상의 원활한 성교의)
   5) 항상 또는 거의 항상

4. 지난 6개월 동안 성생활에 성교를 발표하기 허락해 기대할 만큼 충분히 유지하는 것을 얼마나 하시나?
   0) 모든
   1) 적당히 하였다.
   2) 매우
   3) 안되다.
   4) 약간
   5) 전에 외치어

5. 지난 6개월 동안 성생활을 하셨나요?
   0) 성교를 하지 않았다.
   1) 적당히 하였다.
   2) 매우
   3) 안되다.
   4) 약간
   5) 전에 외치어

감사합니다. 스스로의 향상등급을 어떻게 생각해십니까?

1) 본상
2) 약간
3) 전에 외치어
4) 충분히 만족합니다.
Treatment of erectile dysfunction

• First-line treatment for men with diabetes and ED
  - medical therapy with one or the oral phosphodiesterase type 5 (PDE5) inhibitors

• PDE5 inhibitor
  - sildenafil, vardenafil, tadalafil, udenafil, mirodenafil
  - easy to administer and have a high level of patient acceptability due to their efficacy and few associated adverse events
Action mechanism of PDE5 inhibitor

- PDE5 catalyses the breakdown of cGMP, so its inhibition causes an increase in concentration of cGMP, amplifying the effects of NO release and consequently improving erectile function.
Patients with diabetes are often unresponsive to oral treatment

- Treatment fails in 30-40% of cases due to high frequency of somatic and autonomic neuropathy and peripheral vasculopathy

- Only 40% of unselected patients respond to the administration of sildenafil, even at doses of 100mg

Fedele D et al, Diabetes Care 1997;20:836-43
Secondary therapy

• Intracavernosal injection with papaverine or prostaglandin E1 (PGE1) may be indicated
• Transurethral instillation of PGE1 or vacuum erection devices
• Penile prosthesis
Treatment options should be discussed

- Discussed not only with the patient, but also with his partner, if available

- Optimal treatment strategy should address risk factors and comorbidities of ED associated with diabetes, counsel and educate both the patient and his partner with regard to ED, and initiate medical treatment for ED

- Surgical treatment should be considered if medical treatment fails
Retrograde ejaculation (RE)

- Substantial propulsion of semen from the posterior urethra into the bladder (complete or partial)

![Diagram of Retrograde Ejaculation]

- Bladder
- Urethra
- Prostate
- External urethral sphincter contracts
- Internal urethral sphincter relaxes

Parasympathetic and sympathetic nervous systems are involved.

Bladder:
- Seminal vesicle
- Direction of semen
- Urethra
Retrograde ejaculation (RE)

- Late complication of diabetic autonomic neuropathy
- Reported by about one-third of men with diabetes
- Most common cause of male infertility among this group of patients
Diagnostic management of RE

- Clinical history
- Physical examination
- Post-ejaculatory urinalysis and microbiologic tests

Treatment of RE

• Pharmacotherapy
  - alpha-agonist, anticholinergics, antihistamines
    : increase the sympathetic or decrease the parasympathetic tone of the bladder

• Adverse events: dizziness, sleep disturbance, dry mouth and nausea

• Problem with fertility
  - sperm can be retrieved from post-ejaculatory urine and used for intrauterine insemination
Conclusions

• DM is the cause of some urologic complications, such as bladder dysfunctions, erectile dysfunction, and retrograde ejaculation.

• The increasing prevalence of DM leads us to suppose that such urologic problems in patients with DM will probably become more common in the future.

• Urologic complications can occur in the early stage of DM and often progress in a silent fashion.
OAB Syndrome has a Greater Impact on Quality of Life than Diabetes

Kobelt-Nguyen G et al. 27th Annual Meeting of ICS, 1997
Conclusions

• More important to prevent further damage by means of early control

• More awareness and interest are needed to improve our understanding of diabetic complications in urology

• Urologists and diabetologists should ask each other to help them with urologic problem in their patients