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Introductory Chapter: Insights into Urinary Disorders

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1. Introduction

Kidney, ureter, and bladder are the important urinary organs, which not only produce and transport urine, but also play a role as a barrier to prevent the invasion of pathogens [1]. Once any of them has dysfunction or damage, others can be affected. It has been a clinical issue how to prevent these organs from damage.

2. Insight into the dysfunction of kidney and bladder

The foundation protecting the function of these urinary organs is to understand their pathophysiology and risk prediction on a deeper level. Recently, the advances in genomics, proteomics, and metabolomics provide clinicians and researchers with the novel insights into this field.

Membranous nephropathy is one of the most common causes of adult nephrotic syndrome, which presents a significantly high risk to progress to end-stage kidney disease [2]. Its pathogenesis had been unknown until M-type phospholipase A2 receptor (PLA2R) was identified, which confirmed membranous nephropathy was a kind of antibody-mediated autoimmune glomerular disease [3]. Subsequently, thrombospondin type-1 domain-containing 7A (THSD7A) was found as another target antigen in patients with anti-PLA2R-negative membranous nephropathy [4]. Some studies revealed that the level of PLA2R was correlated with the activity of membranous nephropathy and the effectiveness of immunosuppression [5, 6]. Another study showed that the persistence of serum anti-THSD7A antibodies suggested a high recurrence risk of membranous nephropathy in the patients underwent renal transplant [7].

Diabetic nephropathy is another common cause for patients to suffer end-stage kidney disease. Interestingly, not all the patients with diabetes mellitus will eventually develop into diabetic nephropathy. It has been revealed that genetic susceptibility plays a role in pathogenesis of diabetic nephropathy [8]. A number of studies demonstrated some genes including ELMO1, APOC1, ACE, AKR1B1, APOE, CHN2, EPO, GREM1, NOS3, HSPG2, FRMD3, CPVL, VEGFA, CARS, and UNC13B were associated with diabetic nephropathy [9, 10]. Of those, ELMO1 is the most prevalent one associated with diabetic nephropathy risk, which is located on chromosome 7 p14.1–2. The result from a meta-analysis showed the relationship between ELMO1 and diabetic nephropathy exclusively in Asia population with diabetes mellitus [11]. Traditionally, microalbuminuria has been considered as the main standard for early diagnosis of diabetic nephropathy. However, its predictive value for diabetic nephropathy is being questioned because a number of conditions, including hyperglycemia, hypertension, infections, stress, severe sports and cardiovascular decompensation, may contribute to the false-positive result [12]. Furthermore,

microalbuminuria cannot detect the early stage of diabetic nephropathy since its appearance is generally secondary to the glomerular damage [13]. Proteomics provides an insight into the risk prediction of early diabetic nephropathy and prevention of late-stage kidney damage, because not only the structure and function of a series of proteins are analyzed, but also the interaction among proteins is measured. Based on the proteome analysis, several proteins present the predictive value for kidney damage in patients with diabetic nephropathy. Basically, these proteins can be classified into three groups. Vitamin D-binding protein (VDBP) and neutrophil gelatinase-associated lipocalin (NGAL) are considered as the biomarkers related to tubular damage in patients with diabetic nephropathy. The elevated levels of those proteins in either serum or urine normally indicate potential renal tubular dysfunction [14]. It has been reported that GPC5, ANGPTL4, and soluble Klotho could be the biomarkers detecting glomerular damage [14]. Additionally, MCP-1, as an inflammation-related biomarker, has been used to predict the development of diabetic nephropathy [14].

Besides kidney diseases, interstitial cystitis/bladder pain syndrome (IC/BPS) is a common bladder storage dysfunction, which causes patients severe storage lower urinary tract symptoms (LUTS). Currently, the exact etiology of IC/BPS is still not fully understood and no gold standard is available for the diagnosis of IC/BPS. With the development of proteomics and metabolomics, a set of urine biomarkers associated with IC/BPS were found, which allows clinicians to understand IC/BPS at the molecular level. Tonyali et al. found that IC/BPS patients presented a significantly higher level in urinary nerve growth factor (NGF) normalized to urine creatinine compared with healthy controls [15]. Macrophage inhibitory factor (MIF) is another potential biomarker, which was found to be significantly increased in IC/BPS patients in comparison with control groups. Its reported sensitivity, specificity, and AUC in detecting IC/BPS were 47%, 91% and 0.730, respectively, using MIF normalized to urine creatinine [16]. In addition, Parker et al. [17] identified six metabolites associated with IC/BPS using liquid chromatography-high-resolution mass spectrometric. Of those, etiocholan-3 α -ol-17-one (Etio-S) was considered as a good predictor for IC/BPS, with a sensitivity of 91.2%, a specificity of 87.4%, and AUC of 0.92.

3. A powerful barrier to pathogen invasion

Apart from urine transport, storage, and elimination, kidney, ureter and bladder also act as a barrier preventing pathogens from invading. On one hand, intact urothelium and normal anatomical structure and function of urinary tract are the foundation of a powerful barrier. Any anatomical or physiological abnormality related to urinary system may weaken the barrier, which makes the body vulnerable to pathogens. On the other hand, evolution of bacterial virulence and acquisition of antibiotic resistance make the pathogens more invasive. Once the host defense is not strong enough to resist microbial attack, the body will suffer from urinary tract infection (UTI).

Bladder outlet obstruction is one of the most common anatomic abnormalities of lower urinary tract, which significantly increases UTI risk [18]. In general, the causes of bladder outlet obstruction include urethral stricture, bladder neck obstruction, and, in men, benign prostatic hyperplasia. Of those, benign prostatic hyperplasia is the most common reason in the aging male population. It is reported that the prevalence of bacteriuria in men with benign prostatic hyperplasia ranges from 4.4 to 44.7% [19]. According to some guidelines, recurrent or persistent UTI is considered as an indication for surgical treatment in men with benign prostatic hyperplasia [18, 20].

Vesicoureteral reflux (VUR) is a common congenital anatomic abnormality in children, which is closely associated with high risk of UTI. The prevalence of VUR is approximately 1% in general population and is significantly increased in children [21, 22]. It is reported that 30 ~ 40% of children with VUR experience recurrent UTI [23]. VUR is graded from I (mild) to V (severe) based on the height of reflux up the ureter and degree of dilatation of the ureter. The higher grade the VUR is, the higher risk the patients develop renal failure in future due to the renal scars secondary to UTI. Therefore, it is important to prevent and manage UTI in patients with VUR. Traditionally, antibiotic prophylaxis has been considered as an effective strategy to prevent UTI in patients with VUR. However, a meta-analysis including four randomized controlled trials (RCTs) did not demonstrate a clear benefit of antibiotic prophylaxis in children with grades I and II VUR [24]. Although a later meta-analysis including eight RCTs showed the effectiveness of antibiotic prophylaxis in preventing recurrent UTI, the majority of the studies were at high risk of bias, which significantly weaken the certainty of evidence [25]. Surgical correction is a therapeutic strategy for high grade of VUR with a successful rate of 80 ~ 93% [26, 27].

Besides anatomic defects, the physiological abnormalities resulting from a series of conditions, such as pregnancy, diabetes mellitus, and renal failure, can also cause the body to be susceptible to UTI. Of those, pregnancy is the most common reason resulting in the temporary physiological abnormalities in women. On one hand, the enlarged uterus during pregnancy may compress the bladder and ureter, causing ureteral dilation and hydronephrosis. On the other hand, the changes in hormone levels stemming from the pregnancy can induce the relaxation of ureteric smooth muscles, which contributes to the urine retention in the renal-collecting system and ureter. As a result, the dilated renal pelvic and ureter provide a permissive environment for pathogens to grow and reproduce. In general, the prevention of UTI in these cases should be based on the management of the coexisted conditions.

With the broad-spectrum antibiotics being widely used, the bacteria continue to evolve *via* developing various defense mechanisms. In general, bacterial pathogens can achieve drug resistance through three different biochemical pathways [28]. Firstly, bacteria can mutate genes encoding the target site of antibiotics and consequently survive in the presence of the antimicrobial molecule. Secondly, bacteria can upregulate the expression of efflux pumps, which result in antibiotic resistance due to extruding the drug out of the cell. Finally, bacteria can produce some special proteins that interfere with the target site the antibiotics act on. In terms of specific bacteria, *Escherichia coli* producing extended spectrum beta-lactamases (ESBL) is the most common drug-resistant pathogen causing refractory UTI. Although there are no specific data regarding the prevalence of ESBL-positive *E. coli* in UTI, the percentage of ESBL-positive *E. coli* isolated from bloodstream showed a significantly increase over the past years [29]. The management for UTI caused by ESBL-positive *E. coli* remains a challenge since the majority of antibiotics have no effect on the drug-resistant pathogen. Based on current evidence, fosfomycin trometamol appears to be a therapeutic option because of its broad spectrum of activity against both Gram-negative bacteria.

4. Summary

With the development in genomics, proteomics, and metabolomics, a series of findings bring some novel insights into the pathophysiology and potential etiology of urinary tract disorders, which allows clinicians to perform personalized treatment for patients. Besides, a number of recent studies, which reveal host susceptibility factors and changes in bacterial virulence, provide important information for clinicians in making prevention strategies for UTI.

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