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Review Article



Role of Nervous System In urinary Bladder and Diabetes Mellitus: Review

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ABSTRACT

Urinary bladder is a hollow, collapsible, smooth muscular organ shaped like a balloon, which is a part of the urinary system. The walls of urinary bladder consists of four layers namely mucosa, submucosa, muscularis and the serosa. The function of urinary bladder is to relax and store urine during filling and to contract forcefully in order to empty the bladder during micturition. The nervous system monitors and controls almost every movement of urinary bladder through a series of positive and negative feedback loops. Diabetes mellitus (DM) is a rampant epidemic worldwide. DM affects more than 285 million people worldwide in 2010 and it estimated that it would affect 439 million by the year 2030. This review focuses on pathophysiological mechanisms responsible for urologic complications of diabetes and emphasizing on recent developments in our understanding of this condition. We also tried to shed some light on molecular biology which takes place during diabetes mellitus urinary bladder complications.

Keywords: Urinary bladder detrusor muscle, Role of nervous system, Excitation-contraction coupling, Diabetes, Diabetic neuropathy, Diabetic retinopathy, Diabetic nephropathy.

INTRODUCTION

Development and Structure of Urinary Bladder

In the fetus, development of the urinary bladder starts around the 8th week when it differentiates into smooth muscle and transitional epithelium. Urinary bladder is developed from the intermediate mesoderm of the fetus. The fetal bladder starts filling with urine by about 10 weeks. The bladder fills and empties approximately every 60 minutes. The fetal urinary production is approximately 15 mL/hr at 30 weeks, which reaches 30 mL/hr towards the end of pregnancy. It empties every 30-60 min. The size of the bladder varies over a large range between species. For mouse and rat, the bladder capacity is 0.15 mL and 1 mL respectively.¹

Urinary bladder is a hollow, collapsible, smooth muscular organ shaped like a balloon, which is a part of the urinary system. Initially, at birth in infants the bladder is relatively in higher position than in the adult. It is in the abdominal rather than pelvic, extending about two-thirds of the distance towards the umbilicus. It progressively lowers down and reaches to the adult position shortly after the puberty.² The dimension of urinary bladder varies according to the differing in the urine content and sex of the animal or human. In females, urinary bladder is smaller because the uterus occupies the space just superior to the urinary bladder.³ A moderately full bladder is 12 cm long but it can become double the size if necessary. Although urine is produced daily, it can be stored in the bladder until its release is convenient. In males, urinary bladder is directly anterior to the rectum while in females, it is anterior to the vagina and inferior to

the uterus. In females, urinary bladder is a continuation of the uterus.⁴

Urinary bladder is made up of several parts namely - dome, body, fundus and the neck. The body and fundus of the urinary bladder is highly mobile and highly distensible and have the capacity to expand into abdomen according to the volume of urine. In contrast, bladder base is relatively indistensible.⁵ The folds of the peritoneum hold the urinary bladder in position. The apex of urinary bladder is superior to the pubis symphysis whereas the fundus is a triangular and postero-inferior. There is no special constriction in the neck of the bladder.² In males, it is in direct continuity with the base of prostrate whereas in females it related to the pelvic fascia, which surrounds the upper urethra. In both sexes, the superior surface is covered by peritoneum but the posterior surface lacks peritoneum.³

The urinary bladder empties into the urethra, which is a continuation of the neck, where the uterus enters the urinary bladder and urethra joins the bladder forming the trigone on the mucosa.² When empty, the bladder collapses into its pyramidal shape where its muscular walls are thick and contains rugae. However as bladder is filled with urine it becomes spherical and the muscular wall becomes thinner and rugae disappear as the volume further increases and bladder becomes pear shaped. Both openings of uterus have valves, which are made up of mucosa to prevent back flow from the bladder to the ureters. There are three openings in the floor of the urinary bladder. Two of the openings are from the ureters and form the base of the trigone. The third opening is at the apex of the trigone that opens into the urethra. A



band of the detrusor muscle encircles this opening to form the internal urethral sphincter.³

Detrusor Muscles in Urinary Bladder

In human detrusor, there are bundles of muscle cells of varying size, which are surrounded by connective tissue and they are rich in collagen. These bundles vary extensively in size. In the human detrusor, they are large, a few millimeters in diameter and are composed of several smaller sub-bundles. These bundles are not clearly arranged in distinct layers, but run in all directions. Cells with long dendritic processes can be found parallel to the smooth muscle fibers. These cells contain vimentin as an intermediate filament protein which is expressed by cells of mesenchymal origin and non-muscle myosin.⁶

The individual muscle cells in the detrusor are typical smooth muscle cells. They are long, spindle-shaped cells with a central nucleus. When fully relaxed, the cells are several hundred microns long and the widest diameter is 5–6 μm . The cytoplasm packs with the normal myofilaments and the membranes contains regularly spaced dense bands with membrane vesicles. There are also scattered dense bodies in the cytoplasm.⁷

Urinary Bladder Wall

The walls of urinary bladder consists of four layers namely mucosa, submucosa, muscularis and the serosa. The mucosa is the innermost layer, which has a structure similar to the uterus. This layer is very thick and smooth containing transitional epithelium.⁸ Surrounding the mucosa, submucosa layer is present. The second layer in the walls is the submucosa that supports the mucous membrane. It is composed of connective tissue with elastic fibers. The next layer is the muscularis, which is composed of smooth muscle. The smooth muscle fibers are interwoven in all directions and collectively called detrusor muscle. Contraction of this muscle expels urine from the bladder.³ The serous layer is the outermost layer. It is found only on the superior surface of the bladder. It is actually a continuation of the peritoneum.²

Functions of the Urinary Bladder

The function of urinary bladder is to relax and store urine during filling and to contract forcefully in order to empty the bladder during micturition. The urinary bladder functions as a transient reservoir for urine and various solutes with the capacity to hold up to 700 -800 mL of urine which is brought from kidney through ureters.⁹ Storage of urine occurs at a low pressure. During filling of the urinary bladder, the smooth muscle cells have to relax, elongate and rearrange in the wall over a very large length interval. Disturbances of the storage function may result in lower urinary tract symptoms (LUTS) such as urgency, frequency and urge incontinence are the components of the overactive bladder syndrome. LUTS is marked with age in both males and females and is a major problem in the elderly population. The overactive bladder syndrome is due to involuntary contractions of

the smooth muscle of the bladder during the storage phase.¹⁰

Urine is expelled from the urinary bladder and ultimately from the body by a process known as micturition. This process is also known as voiding or urination. During micturition, force generation and shortening must be initiated comparatively fast and occurs over a larger length range.¹¹ In adults, this process is under voluntary control. The contractile function of smooth muscle involves the functional interplay of multiple processes including neurotransmitter receptor activation, intracellular Ca^{2+} signalling and ion channel regulation of membrane excitability. Failure at the level of neural regulation or smooth muscle contractile function can lead to incomplete bladder emptying.¹² When the volume of urine in the urinary bladder exceeds 200- 400 mL, pressure within the bladder increases considerably and the stretch receptors in its walls transmit nerve impulses into spinal cord via spino-bulbo-spinal pathway which passes through the relay centre in the brain. The impulses propagate through spinal cord segments S2 and S3 and trigger spinal reflex called 'micturition reflex'. Effective urine voiding is achieved by the complex interaction between coordinated contraction of the urinary bladder detrusor smooth muscle and relaxation by central nervous system (CNS) and peripheral nervous system (PNS).¹³

Innervations of Urinary Bladder

The nervous system monitors and controls almost every organ system through a series of positive and negative feedback loops. The CNS includes the brain and spinal cord while PNS connects the CNS to other parts of the body and is composed of bundles of neurons. The urinary bladder serves two main functions: the storage of urine without leakage and the periodic release of urine. These functions are dependent on central as well as peripheral autonomic and somatic neural pathways.¹⁴

Parasympathetic Nervous System

The parasympathetic nervous system is responsible for major excitatory input to the bladder. This system regulates "rest and digest" functions which means this system controls basic bodily functions. Parasympathetic preganglionic axons originate from the column of the S2 to S4 spinal cord terminates on postganglionic neurons in the bladder wall and in the pelvic plexus. Neurons of PNS emerge from the brainstem as part of the cranial nerves III, VII, IX and X nerve and also from the sacral region of the spinal cord via sacral nerves 2, 3 and 4.⁵ The parasympathetic preganglionic axons release acetylcholine (ACh) which activates postsynaptic nicotinic receptors. Nicotinic transmission at ganglionic synapses can be regulated by various modulatory synaptic mechanisms that involve muscarinic, adrenergic, purinergic and enkephalinergic receptors. Parasympathetic postganglionic neurons in turn provide an excitatory input to the bladder smooth muscle.



Adenosine triphosphate (ATP) is a co-transmitter, which is released from parasympathetic postganglionic terminals and acts on purinergic receptors to induce a rapid contraction of the bladder. Due to the presence of ATP, antimuscarinic agents do not completely abolish evoked bladder contractions in humans.¹⁴

Sympathetic Nervous System

The sympathetic nervous system is a part of the autonomic system that are connected with the spinal roots from the second thoracic (T2) to the second lumbar (L2). Sympathetic nervous system is distributed throughout the body. The sympathetic nervous system controls "fight-or-flight" responses which means the system prepares the body for strenuous physical activity. Most of preganglionic axons are short and synapse with postganglionic neurons within ganglia found in the sympathetic ganglion chains. Sympathetic postganglionic terminals releases norepinephrine to elicit contractions of the bladder base and urethral smooth muscle and relaxation of the bladder body mediated mainly through $\alpha 1$ and $\beta 2$ adrenoceptors.¹⁵

Excitation Contraction Coupling (ECC)

Excitation-Contraction Coupling (ECC) is a process whereby an action potential causes a myocyte to contract. Smooth muscle contraction is initiated by an increase in the intracellular Ca^{2+} concentration. In principle, Ca^{2+} can enter the cytoplasm through the cell membrane via Ca^{2+} channels or released from the sarcoplasmic reticulum (SR). The release of Ca^{2+} from the SR is an important step in activation of the detrusor muscle. The release of Ca^{2+} triggers by inositol trisphosphate (IP_3) via IP_3 receptors and by Ca^{2+} via ryanodine receptors. The Ca^{2+} activation of the contractile proteins is considered to occur via a phosphorylation pathway where Ca^{2+} binds to calmodulin and the Ca^{2+} /calmodulin complex activates the Myosin Light-Chain Kinase (MLCK) which catalyzes the phosphorylation of the 20-kDa myosin regulatory light chains on serine at position 19. This MLCK uses ATP to add a phosphate group to a portion of the myosin head. Once the phosphate group is attached myosin head starts to bind with actin and after that contraction occurs. After contraction, Ca^{2+} moves slowly out of the muscle fibre, which delays contraction. The prolonged presence of Ca^{2+} in the cytosol provides a state of continued partial contraction. Contraction in smooth muscle fibre starts more slowly and lasts much longer than skeletal muscle fibre contraction. Another difference is that the smooth muscle can shorten and stretch more than other muscle type.⁴

Role of Calcium in Smooth Muscle Contraction

By increasing the intracellular Ca^{2+} concentration, smooth muscle contraction initiated. There is 10,000-fold difference in the Ca^{2+} concentration between the extracellular and intracellular medium of the cell. SR, mitochondria and plasma membrane are the sites in the

smooth muscle from where calcium can be released or accumulated. Smooth muscle contraction is initiated by an increase in the intracellular Ca^{2+} concentration.⁵ In the urinary bladder muscle, various neurotransmitters like acetylcholine are released from motor nerve endings. This acetylcholine binds to specific receptors to activate contraction in smooth muscle. Subsequent to this binding, the typical response of the cell is to increase phospholipase C (PLC) activity via coupling through a G protein. PLC produces two potent second messengers from the membrane lipid phosphatidylinositol 4,5-bisphosphate diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). IP_3 binds to specific receptors on the sarcoplasmic reticulum, which causes release of activator Ca^{2+} .^{16,17} DAG along with Ca^{2+} activates PKC which phosphorylates specific target proteins. In most smooth muscles, PKC has contraction-promoting effects such as phosphorylation of Ca^{2+} channels that regulate cross-bridge cycling. Activator Ca^{2+} binds to calmodulin, leading to activation of myosin light chain kinase. This kinase phosphorylates the light chain of myosin and in conjunction with actin, cross-bridge cycling occurs which start initiating shortening of the smooth muscle cell.^{18,11} This Ca^{2+} can enter the cytoplasm through the cell membrane via Ca^{2+} channels or released from the sarcoplasmic reticulum (SR). The release of Ca^{2+} from the SR is an important step in activation of the detrusor muscle. The Ca^{2+} activation of the contractile proteins is considered to occur via a phosphorylation pathway where Ca^{2+} binds to calmodulin to form Ca^{2+} - calmodulin complex. This complex activates the MLCK which catalyzes the phosphorylation of the myosin regulatory light chains. The Ca^{2+} induced activation of MLCK and the MLCP activity are the main pathways for contraction and relaxation. Ca^{2+} concentration and myosin light-chain phosphorylation is variable in the muscle. The phosphorylated myosin interacts with the actin filaments to form cross- bridges. The cross- bridges between actin and myosin continue if the intracellular calcium is maintained but if there is some declination of Ca^{2+} , the enzyme myosin phosphatase is activated.¹¹ As a result, appropriate contraction occurs in urinary bladder muscles.

Relaxation of the Smooth Muscle of Urinary Bladder

Smooth muscle relaxation occurs as either a result or removal of the contractile stimulus or by the direct action of a substance that stimulates inhibition of the contractile mechanism.¹⁸ The process of relaxation requires a decreased intracellular Ca^{2+} concentration and increased MLC phosphatase activity. Decreases in the intracellular concentration of Ca^{2+} elicit smooth muscle cell relaxation. Ca^{2+} uptake into the sarcoplasmic reticulum is dependent on the ATP hydrolysis. This sarcoplasmic reticular Ca, Mg-ATPase when phosphorylated binds to two Ca^{2+} ions which are then translocated to the luminal side of the sarcoplasmic reticulum and released.¹⁹



$\text{Na}^+/\text{Ca}^{2+}$ exchangers are also located on the plasma membrane and aid in decreasing intracellular Ca^{2+} . During relaxation, receptor- and voltage-operated Ca^{2+} channels in the plasma membrane close resulting in a reduced Ca^{2+} entry into the cell. Mg^{2+} also necessary for the activity of the enzyme binds to the catalytic site of the ATPase to mediate the reaction. The plasma membrane also contains Ca/Mg-ATPases which provides an additional mechanism for reducing the concentration of activator Ca^{2+} in the cell. This enzyme differs from the sarcoplasmic reticular protein in that it has an auto inhibitory domain that can be bound by calmodulin; causing stimulation of the plasma membrane Ca^{2+} pump.²⁰

Diabetes Mellitus

Diabetes mellitus (DM) is a disease that was recognized in antiquity. The term “diabetes mellitus” was first used in the 18th century to distinguish the sweet taste of diabetic urine from other polyuric states in which the urine was tasteless. The first major breakthrough in the history of this disease occurred in 1921 when Banting and Best discovered insulin.²¹ Diabetes mellitus (DM) is a condition in which the pancreas no longer produces enough insulin or when cells stop responding to the insulin that is produced due to which glucose in the blood cannot be absorbed into the cells of the body this leads to hyperglycemia in the urine.²²

DM is a syndrome with metabolic, vascular, and neuropathic components that are all interrelated. The metabolic syndrome is characterised by alterations in carbohydrate, fat, and protein metabolism. The body's primary energy source is glucose which is obtained from the digestion of foods containing carbohydrates. Glucose from the digested food circulates in the blood as a ready energy source for any cells. Insulin is a chief hormone produced by cells in the pancreas. Insulin binds to a receptor site on the outside of cell and acts like a key to open a doorway into the cell through which glucose can enter. Some of the glucose can be converted to concentrated energy sources like glycogen or fatty acids and saved for later use. When there is not enough insulin produced or when the doorway no longer recognizes the insulin key, glucose stays in the blood rather than entering the cells.²³ Diabetes and urologic diseases are very common health problems that markedly increase in prevalence and incidence with advancing age. Diabetes is associated with an earlier onset and increased severity of urologic diseases that results in costly and debilitating urologic complications. Urologic complications, including bladder dysfunction, sexual and erectile dysfunction, as well as Urinary Tract Infections (UTIs), have a profound effect on the quality of life of men and women with diabetes.²⁴

Diabetes mellitus (DM) is a rampant epidemic worldwide. DM affects more than 285 million people worldwide in 2010 and it estimated that it would affect 439 million by the year 2030.²⁵ Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million

diabetic individuals currently diagnosed with the disease.²⁶ In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively.²⁷ The prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.²⁸

Diabetes can be classified into two different forms –

Type I diabetes mellitus also known as insulin- dependent diabetes (IDDM) or juvenile diabetes.

Type II diabetes mellitus is known as non- insulin-dependent diabetes (NIDDM) or adult onset.²⁹

Type I Diabetes Mellitus (IDDM)

This accounts for only 10-15% of all cases of diabetes. Result from a study of 27 countries showed that the incidence of type I diabetes is on the rise by around 3% per year.³⁰ Type I diabetes can be subdivided into a) Autoimmune and b) Idiopathic form. The autoimmune form is by far the most common and results from a cell-mediated autoimmune destruction of the pancreatic beta cells. Type I DM is a slowly progressive thyroid T cell – mediated autoimmune disease including thyroid disease, Addison's disease and vitiligo. In Type I diabetes, the body produces little or no insulin. This diabetes found in younger peoples, less than 40 years old.^{31,32} Under this condition, patient needs exogenous insulin to reverse catabolic condition, prevent ketosis and decreases hyperglucagonemia.²⁹ If anybody has type I diabetes, they require regular insulin injections for the rest of life in order to keep your glucose levels normal. Insulin injections can be administered using injection pen. Most people need either 2-4 injections a day. An alternative to injecting insulin is insulin pump therapy. The intense insulin therapy with glargine which is biosynthetic insulin is used to give lower fasting blood glucose as compared with fever episodes of hypoglycaemia as compared with twice daily Neutral Protamine Hagedorn insulin (NPH) in patient with type I diabetes.³³ A small proportion of patients with type I diabetes will fall into the idiopathic form.³⁴ This form of diabetes is strongly inherited caused by decreased insulin secretion and lacks immunological evidence for autoimmunity.

Type II Diabetes Mellitus (NIDDM)

Type II DM is more complex condition than type I DM because there is a combination of resistance to the action of insulin in liver and muscle together with impaired pancreatic β - cell function which leads to insulin deficiency.³⁵ Type II DM is principally a disease of middle – aged. In United Kingdom, it affects 10 % of the population over 65 and over 70 % of all cases of diabetes occur after



the age of 50 years.³¹ The prevalence of type II DM increases with age but varies between different populations. The prevalence is higher in certain ethnic groups: South Asians and Afro-Caribbean's have sixfold higher risk compared to white populations.³⁶ Diabetes can not be cured but it can be kept in control to prevent health problems later in life. If anybody has type II diabetes, they have to lose weight, make changes in their diet and taking regular exercise. Sometime people with type II diabetes require tablets insulin injections.²² Eber Papyrus was the first person who listed the symptoms of disease. DM is one of the leading causes of morbidity and mortality in the world with long term effects of blindness, renal damage and particularly cardiovascular and cerebrovascular disease (Table 1).³⁷

Table 1: Showing the symptoms of Diabetes Mellitus in Type I and Type II.

Symptoms	Type I	Type II
Hunger	Yes	Yes
Onset	Fast	Slow
Thirst	Yes	Yes
Tiredness	Yes	Yes
Polyuria	Yes	Yes
Bed Wetting	Yes	No
Mood Changes	Yes	Yes
Weight Loss	Yes	Yes
Visual Disturbances	Yes	Yes
Thrush Infection	Yes	Yes
Boils	Yes	Yes
Pain	No	Yes
Unexplained Symptoms	Yes	Yes
Occasional Abdominal Pain	Yes	No

Diabetic patients have a normal life style but its late complications results in reduced life expectancy and major health costs. These include diabetic neuropathy, diabetic retinopathy and coronary heart disease.²⁷

Long-term complications

Long-term complications of DM occur in both forms of condition in humans and have an important role in the increased morbidity and mortality suffered by these individuals. Macrovascular complications include coronary heart disease, atherosclerosis, and peripheral vascular disease. Microvascular complications include retinopathy, nephropathy and neuropathy.³² Over 50% of men and women with diabetes have bladder dysfunction.²⁴ Diabetic neuropathy is the most common complication of this disease and its manifestations can be divided into two broad categories, somatic (peripheral) and visceral. Disease of the large and small vessels results in myocardial infarction, stroke and gangrene of the lower extremities.

Diabetic Neuropathy

Diabetic neuropathies are complex, heterogeneous disorders that encompass a wide range of abnormalities affecting both peripheral and autonomic nervous systems. Diabetes causes various nerve disorders. Diabetes neuropathy is a common complication of insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM). Diabetic neuropathies cause numbness and sometimes pain as well as weakness in the hands, arms, feet and legs. Neurological problems in diabetes may occur in every organ system including the digestive tract, heart and genitalia. Diabetic neuropathy affects approximately one-third people of DM which disrupts the nerve supply to the bladder. This may increase involuntary bladder contractions and decrease bladder sensation. With severe neuropathy, function of the detrusor muscle may be affected. Diabetic neuropathies are classified as peripheral, autonomic, proximal, and focal. Peripheral neuropathy is a generalized sensorimotor polyneuropathy of gradual onset that is usually progressive. It is the earliest and most widely recognized form of diabetic neuropathy which affects the lower limbs. Patients initially experience sensory manifestations. Loss of deep tendon reflexes and poor sensation can also be present. Poor sensation in the feet can lead to foot problems and may contribute to the development of diabetic ulcers. Involvement of motor fibres can cause muscle weakness and atrophy leading to feet deformities, which may also contribute to ulcers.^{38,39} Autonomic neuropathy causes changes in bladder function, digestion, sexual response and can also affect the nerves that serve the heart and control blood pressure but symptomatic autonomic neuropathy is rare. In autonomic neuropathy, male erectile dysfunction is more common. Erectile dysfunction in diabetes has many causes including anxiety, depression, alcohol excess and drugs. Proximal neuropathy causes pain in the thighs, hips which causes weakness in the legs. Focal neuropathy results in the sudden weakness of one nerve or a group of nerves due to which muscle weakness or pain occurs. Due to neuropathy, loss of tone, incomplete emptying can occur resulting in an atonic, painless and distended bladder.²⁷

Diabetic Retinopathy

Diabetic retinopathy and blindness from diabetes became a significant problem after the discovery of insulin in 1922 due to the increase in the life expectancy of diabetics. Diabetes causes various changes in the retinal circulation, causing two forms of retinopathy: non-proliferative and the most severe proliferative retinopathy.³¹ In United Kingdom, 5 % of population become blind in past after 30 years of diabetes. Diabetes causes increased thickness of capillary basement membrane and increased permeability of the retinal capillaries.²⁷ Ongoing damage leads to blood vessels becoming leaky which results in loss of blood. Some blood vessels lead to ischemia and release of growth factor that stimulate formation of new blood



vessels. These blood vessels lack the supportive connective tissue and have high risk of haemorrhage due to which sudden loss of vision occurs.³⁶ After 20 years of type I diabetes almost all patients have retinopathy while 50- 80% of patients with type II diabetes will have retinopathy. Retinal photocoagulation is an effective treatment particularly if it is given in early stage when patient is symptom less. Without treatment 50% of patients become blind within 5 years. Regular screening for retinopathy is essential in all diabetic patients.²⁷

Diabetic Nephropathy

Diabetic nephropathy occurs in approximately one third of both types of diabetics.⁴⁰ It can be divided into 5 stages. Stage I occurs at the onset of the disease and is characterised by 30%-40% increase in the glomerular filtration rate (GFR) above normal. Other changes are increase in kidney size, increased glomerular diameter, and tubular size.²⁷ Stage II is characterised by normal excretion of albumin regardless of the duration of the diabetes. Stage III or incipient diabetic nephropathy is characterised by microalbuminuria at rest, which can be detected by a sensitive method such as radioimmunoassay. Stage IV or overt diabetic nephropathy is characterized by clinical proteinuria and even higher blood pressure than stage III. The development of proteinuria and decreased GFR identify end-stage renal disease.^{41,42}

CONCLUSION

Diabetic bladder dysfunction is relatively common and can have different manifestations from detrusor instability to poor bladder sensation and contraction. Diabetic neuropathy plus detrusor muscle and urothelial dysfunctions all have some role in pathophysiology. Although scientist explored a lot of pathogenic mechanisms of lower urinary tract dysfunction in diabetes. There is still lacking of effective screening and treatment strategy regarding diabetes.

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