Review Article

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Understanding underactive bladder: a review of the contemporary literature

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Abstract

Underactive bladder (UAB) is characterized by prolonged voiding, hesitancy, and slow and/or intermittent stream with or without a sensation of incomplete bladder emptying. The overlap of UAB lower urinary tract symptoms with those of overactive bladder or bladder outlet obstruction, as well as its multifactorial etiology, make UAB study, as well as its diagnosis and management, a very arduous and challenging task. Therefore, despite its incidence and significant impact in the quality of life of both men and women, UAB remains a poorly understood urologic condition with insufficient and ineffective treatment options available. In this review, we will focus on the etiology theories that have been proposed and the animal models available to test those theories.

Keywords: animal model, current treatment options, lower urinary tract symptoms, multifactorial pathogenesis, underactive bladder

Introduction

Underactive bladder (UAB) is defined by the International Continence Society as a symptom complex characterized by a slow urinary stream, hesitancy, and straining to void, with or without a feeling of incomplete bladder emptying, sometimes with storage symptoms.[1] UAB diagnostic is based on clinical symptoms, contrary to detrusor underactivity (DU), whose diagnostic hinge on urodynamic studies.[2] According to the International Continence Society, DU is "a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span".[1] Even though DU may often occur alongside UAB in many patients, in this review we will focus on UAB.[1–3]

Despite being a relatively common diagnostic reported in both men and women, UAB has received minimum attention until recently, mainly due to the lack of consensus on the definition and the absence of standardized diagnostic criteria.[2,4] Thus, UAB remains a relatively underresearched condition with insufficient and ineffective treatment options available.[4,5]

The diagnostic of UAB is quite difficult and challenging due to the overlap of lower urinary tract (LUT) symptom with those of overactive bladder and bladder outlet obstruction (BOO), often leading to the misdiagnose of UAB patients.[3,4] Moreover, the clinical observation of UAB occurrence in different patient groups suggests that UAB presents a multifactorial etiology, making its clinical diagnostic even more difficult.[6] Consequently, the absence of an accurate diagnostic not only makes the true scale estimation of UAB a complicated process, as also hinders its treatment.[7]

Therefore, to overcome this and ensure a better quality of life for patients, further studies are needed to enhance understanding of UAB and thus, to develop more effective treatment options.[7]

Etiology

Normal bladder filling (storage) and periodic bladder emptying (voiding) depend of the coordination of 2 components of the LUT, the urinary bladder (the reservoir), and the urethral outlet (which includes the bladder neck, the urethra and the urethral sphincter).[8] This process is closely regulated by a complex neural control system which acts by circuits of on-off switching, specifically situated in the brain, the spinal cord and the peripheral ganglia.[8,9] The voiding reflex is mediated by a spinobulbospinal pathway that passes through the pontine micturition center (PMC), which consists of a coordination center located in the rostral brainstem.[10] In fact, PMC is the responsible for establishing the volume upon which the LUT switches over the filling mode to the emptying mode, thus defining the bladder capacity threshold.[11] As a result, PMC stimulation leads to activation of descending pathways that promote urethral sphincter relaxation, immediately followed by increased sacral parasympathetic activity.[10] This process results in contraction of bladder detrusor and, consequently, in increasing intravesical pressure, promoting the urinary flow.[8,9] Therefore, because of the complexity of the neuromuscular mechanisms involved in the voiding process control, any disturbance that may occur in the pathway, such as several injuries or diseases, may result in impairment of detrusor function and consequently, in the onset of UAB.[8,12]

In clinical practice, UAB presents itself, most of the times, as a multifactorial condition, being a sign and/or result of various pathologies.[13,14] In fact, it turns out that not only pathologies

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vary between patients, as also more than 1 pathology can be responsible for the onset of UAB in a single patient, making the identification of the most relevant targets for treatment a difficult process. Etiological factors resulting in UAB are frequently divided into 3 categories: idiopathic, neurogenic, or myogenic.[15]

Idiopathic etiology

Idiopathic UAB is the term used to designate UAB related to the aging process or UAB resulting of unknown causes in younger patients. Patients with idiopathic UAB present no evident neuropathy or signs of functional or anatomic BOO. Moreover, they show a low or even absent detrusor pressure (Pdet), a maximum flow rate (Qmax) of less than 10 mL/s, a large postvoid residual (PVR) volume (of more than 150 mL) or even urinary retention.[12]

There is current evidence that several changes occur in the LUT with increasing age.[16,17] Human urodynamic studies have reported impaired bladder contractility and voiding efficiency with aging, leading to the development of UAB in many elderly people.[18,19] This bladder impairment is often associated with structural changes occurring in the detrusor, including decreased axon density, which results in impaired autonomic bladder innervation, and increased collagen deposition, with increasing of fibrosis.[20,21] Moreover, other studies have reported that, along with these morphological changes, aging is also associated with a diminished sensory function, which may contribute to the development of UAB in the elderly. This sensory impairment may result in reduction of the bladder sensation, leading to a rise of the bladder capacity threshold and a delay in the voiding desire, proceeded by urgency and impaired bladder emptying.[20,22] Consequently, older individuals commonly show a large PVR volume.[23] Furthermore, several studies have also reported that the detrusor contraction strength, the detrusor pressure at maximum flow, and the maximum flow rate, all decrease with aging, suggesting a gradual impairment of detrusor performance.[24]

Nevertheless, there are various risk factors that may increase the occurrence of UAB in elderly individuals (such as BOO and medications) making it difficult to understand the role of aging in the onset of this disease.[20]

Neurogenic etiology

The development of UAB may be due to damage in the bladder afferent pathways, bladder efferent pathways, or in the lumbosacral spinal cord.[25] Currently, a status of great importance is attributed to the neural mechanisms controlling the voiding process, especially regarding the afferent pathways.[20] These are responsible for monitoring bladder filling volume and their integrity is crucial for the efficiency of detrusor contraction. Therefore, any disturbance that may occur in these nerves can cause loss of bladder volume sensitivity, reduction of detrusor contraction strength, or even the early ending of the voiding reflex, compromising the efficiency of the voiding process.[11,26]

Patients with neurologic disorders such as stroke, Parkinson disease, and multiple sclerosis; diabetes mellitus (DM); and traumatic injuries may develop UAB.[16,27] Several investigations have already described the role of DM) as a common cause of LUT diseases, including UAB.[5,27] Diabetic bladder dysfunction (DBD), commonly known as diabetic cystopathy, represents one of the most frequent complications of DM, and is described as impaired bladder sensation with increased capacity, reduced contractility, and increased PVR urine volume.[16,20] The hyperglycemia associated to DM can cause neuronal damage through mechanisms that involve the polyol pathway activation, increased free radicals generation, protein kinase C activation, and increased advanced glycated end-products formation.[28] Consequently, these metabolic disturbances may lead to autonomic neuropathy due to axonal degeneration and segmental demyelination, thus resulting in reduction of the bladder sensation and, consequently, in impairment of the voiding efficiency. Furthermore, DM is also associated to a diminished synthesis and transport of the nerve grown factor, which may impair sensory nerve function, resulting in an increased PVR urine volume and bladder capacity.[12,28] In addition, apart from diabetic cystopathy, diabetic neuropathy may indirectly affect bladder function. Gastrointestinal complications, including constipation, impaired rectal sensation, and fecal incontinence (resulting from abnormal internal anal sphincter tone), greatly increase the strain required to defecate. Consequently, this straining can lead to weakening of the pelvic muscles and cause bladder and rectal prolapse, increasing the risk of stress incontinence and impaired bladder emptying.[28]

Myogenic etiology

The myogenic etiology of UAB involve changes in the normal structure and/or function of myocytes or their surrounding matrix, compromising not only the generation but also the transmission of detrusor contraction. Myogenic factors may lead to a decreasing of the muscle:collagen ratio, increasing of the space between muscle cells or even to the reduction of muscarinic M3 receptors. These changes may compromise the cellular mechanisms that are essential to myocytes contraction, such as ion storage and/or exchange, excitation-contraction coupling, calcium storage, or even energy production.[20,29] Therefore, even if the neural pathway is unimpaired, any disturbance that may alter detrusor myocytes properties can result in impairment of detrusor contraction, and consequently in the onset of UAB.[30]

Currently, myogenic factors causing UAB include BOO and again DM.[5] BOO is associated to an increase of the outlet resistance, followed by bladder distension due to the rise of intravesical pressure.[13] In an initial phase, detrusor muscle undergoes compensatory hypertrophy and hyperplasia in an attempt to reduce intravesical pressure and the outlet resistance, and thus maintain the periodic expulsion of urine (compensatory stage). However, in a later phase, the bladder becomes unable to properly compensate (decompensated stage). At this stage, bladder contractile response declines, resulting in the development of UAB. It is thought that this decompensation stage may be due to cyclic ischemic and reperfusion injury, resulting in generation of reactive oxygen species and release of free intracellular calcium. This, in turn, leads to activation of protease and phospholipase, resulting in peroxidation of the lipidic membrane. As a result, both cellular and subcellular membranes of myocytes and neuronal cells may be impaired, consequently leading to decrease of detrusor contractile capacity, as well as denervation.[12,13,20]

In addition, another myogenic factor that plays a significant role in the onset of UAB is DM.[5] DM may affect detrusor muscle function through disturbances of intercellular connections and cell excitability, in intracellular signaling and in receptors density and distribution.[13,28] Furthermore, glucosuria and osmotic diuresis associated to this disease can lead to bladder overdistension and increased intravesical pressure, causing compen-

satory detrusor muscle hypertrophy and promoting an increased PVR urine volume, following decompensation.[12,28] Also, the accumulation of free radicals associated to DM progression can cause myocytes damage, which will clinically manifest as reduced bladder sensation, impaired bladder emptying, and decreased voiding efficiency.[13] Regardless of the etiology of UAB in patients with DM, the early diagnostic and treatment of this disease may be essential to the prevention of UAB symptoms.[12]

Treatment of underactive bladder

There is currently no standard protocol for the treatment of UAB that allows an effective prevention of possible complications commonly associated to this condition or that promote a considerable improvement in the quality of life of patients.[5] The highest priority has been to increase the compliance of patients with UAB to treatment, to minimize the risks related to an incomplete bladder emptying, such as recurrent urinary tract infections, bladder stone formation, and renal impairment.[5,31,32] Patients may benefit from conservative methods, clean intermittent catheterization, pharmacotherapy, surgical treatments, and some promising new alternatives such as stem cell and gene therapies.[5] The selection of the appropriate treatment option hinge on different factors, such as the etiology, age, sex, patient choice, and surgeon experience, among others.[27,32]

Conservative methods and clean intermittent catheterization

Conservative management of asymptomatic patients or patients without high-risk features includes a period of observation before any further treatment.[33,34] Considering that bladder dysfunction does not reveal any signs at the initial stages, it is essential that patients, even if asymptomatic, are continuously monitored, through periodic follow-ups, including urodynamic testing, to detect the disease as early as possible and thus, manage to halt or slow its progress. In fact, this is particularly important in the case of diabetic patients since the reduction of the bladder sensation may turn UAB progression unnoticed.[5]

When applied in symptomatic patients, the common procedure of conservative management includes behavioral modifications such as timed, double or triple voiding, to prevent bladder overdistension and reduce the PVR urine volume.

Crede or Valsalva maneuver is also helpful in stimulating bladder emptying and reducing PVR volume. However, they may increase high intravesical pressure and induce upper urinary tract damage.[35]

Patients who present significant PVR volume and urinary retention may benefit from intermittent urethral catheterization. However, this method, besides increasing the risk of infection, often leads to a decrease in patients' quality of life and an increase of emotional stress.[5,36]

Pharmacotherapy

The available pharmacotherapy to treat UAB aims to improve detrusor contractility. It is based on the premise that by increasing parasympathetic activity, detrusor contraction will also increase.[35]

Parasympathomimetics are agents that increase parasympathetic activity, either by direct stimulation of muscarinic receptors (muscarinic agonists) or inhibition of cholinesterase (cholinesterase inhibitors), thus leading to increased levels of acetylcholine at the muscarinic receptors.[2,34,35] However, these available drugs show limited efficacy in treating this condition, as well as significant adverse effects (including gastrointestinal upset, blurred vision, bronchospasm, and bradycardia).[2,35,36]

Alpha-blockers are substances that decrease urethral muscle tone.[2,36] They are used to reduce symptoms related to BOO.[5,35,36] However, there is no clear evidence of therapeutic efficacy of alpha blockers in the treatment of UAB.[5,34,35]

Intravesical administration of prostaglandin E2 is also a therapeutic intervention that has been studied as a treatment option for UAB. Several studies have suggested that prostaglandin E2 can improve detrusor contraction and promote urethral relaxation. However, this approach also has limited effectiveness in the treatment of UAB.[2,5,33,35]

Acotiamide is a prokinetic drug that increases acetylcholine release and inhibits acetylcholinesterase activity, thus improving parasympathetic activity. The therapeutic effect of this drug was assessed in a small pilot study performed by Sugimoto and coworkers, in which UAB patients were treated with oral acotiamide. This study has evidenced that acotiamide promoted a significant decrease in PVR volume and presented little side effects, which were well tolerated by UAB patients. Thus, acotiamide demonstrated to be a viable drug for UAB treatment. Nevertheless, more studies will be carried out in the future to better evaluate the clinical efficacy of this drug.[36]

In addition, injection of botulinum toxin A in urethral sphincter has also been used in clinical practice as an alternative to treat UAB. The therapeutic effects of botulinum toxin A involve the promotion of urinary sphincter relaxation and decrease of outlet resistance, thus enhancing bladder emptying.[37] However, although this treatment shows significant benefits in a short term, in a long term these benefits are limited.[33]

Surgical treatment

Surgical treatment options for UAB have been used to enhance voiding efficiency and include electrical stimulation, BOO-related surgery, reduction cystoplasty, and latissimus dorsi detrusor myoplasty (LDDM).

Sacral nerve stimulation (SNS), also known as sacral neuromodulation, is the most recognized method of electrical stimulation.[32] SNS modulates pelvic/perineal afferent pathways, resulting in increase of parasympathetic activity in the bladder, and inhibition of sympathetic urethral and somatic sphincter elements of the guarding reflex, which promotes outlet relaxation and improves bladder emptying.[34] SNS has already demonstrated to be effective in selected patients with UAB and is currently applied to treat nonobstructive urinary retention.[5,34,35]

In cases of obstructive urinary retention due to chronic BOO, bladder outlet surgeries may be an appropriate treatment option. Several studies have demonstrated beneficial evidence of transurethral resection of the prostate, prostatectomy with laser energy and transurethral incision of the bladder neck, in patients with both BOO and UAB.[5,35] However, although these treatments options exhibit short-term significant benefits, in a long term these benefits are very limited.[5,31,33,35]

Reduction cystoplasty may be an appropriate treatment option for UAB. This procedure involves the reduction of the bladder capacity which may result in an improved bladder emptying. However, because detrusor contractility remains the same, there is an increased risk of damage the upper tract and of incontinence. For this reason, reduction cystoplasty must be performed exclusively on carefully selected patients.[3,35]

LDDM is another surgery that has been studied as a potential treatment option for UAB. In LDDM the bladder is wrapped with striated muscle to increase intravesical pressure and thus, improve the voiding efficiency. This surgical treatment has showed to be effective on restoring detrusor function, in selected patients with acontractile bladder. However, so far, the long-term effect of LDDM remains unknown.[5,34,35]

Stem cell therapy

Stem cell therapy has the potential to provide novel treatment strategies for a vast range of conditions. In recent years, it has been studied as a promising alternative for the treatment of several urological conditions, including UAB. Because bladder and urethral smooth muscle cells have a limited regeneration capacity, research has been centered attention on muscle regeneration by using multipotent stem cells, rising the smooth muscle and nerve cells proportion, thus enhancing detrusor muscle contractility.[38,39]

Recently, Levanovich and coworkers have performed the first study of autologous muscle-derived stem cells on a single UAB patient 79 years old. Intradetrusor injection of autologous muscle-derived stem cell proved to be safe and, at 3 months, the patient evidenced an enhanced voiding, reduced bladder capacity, and decreased clean intermittent catheterizationCIC necessity. Presently, stem cell therapy for UAB treatment is experiencing a phase 2 in clinical trial.[2,33,39]

Gene therapy

Gene therapy is a method that involves the use of genetic material to alter the cells of a patient, to treat a certain disease.[40] This method is being evaluated as a potential alternative for treatment. Even though gene therapy demonstrates to be a promising UAB treatment option, its application in humans remains under study and is currently restricted to the treatment of life-threatening diseases, like cancer, mainly due to safety concerns. However, with increased gene therapy safety data, it is anticipated that, in the near future, this procedure may be applied in non–life-threatening diseases, like LUT dysfunction.[37] Therefore, gene therapy may represent a promising treatment option for UAB.[40]

Animal Models

Ideal animal models to study UAB pathophysiological mechanisms are those that have an integrative physiology of the LUT, as well as of the voiding neural control similar to humans.[41]

Until now, different animal models of UAB, mainly using rodents, were already described.[9] These models take in consideration UAB different etiologies, as described below.

Idiopathic underactive bladder models

So far, several rodent models have been used to study aging impacts on bladder structure and function, including mice, rats, and guinea-pigs. Like humans, these animal models exhibit complex age-related changes.[42] Various studies using these models have reported symptoms resembling those seen in elderly patients, including impaired detrusor contractility, increased PVR volume, and diminished voiding efficiency, indicating an impaired bladder emptying.[20,42] Moreover, aged mouse and rat models also show decreased bladder volume sensitivity and increased voiding pressure threshold, which is suggestive of an impaired afferent activity.[41,42]

The urinary bladder of older patients with UAB present structural changes, including decreased axons density and increased deposition of collagen on the bladder wall, leading to increasing of fibrosis. Likewise, several animal studies have showed increased fibrosis in the bladder of aged rodents as well.[42] Although those structural and functional changes are similar to those seen in humans, there are inconsistent data on these age-related changes, not only between species, strain, and sex, but also according to the methodology employed.[42,43]

Neurogenic underactive bladder models

Neurogenic UAB models can be divided into peripheral and central models. Peripheral models correspond to those resulting from direct impairment of the bladder, its peripheral innervation or its blood supply and include ischemia/oxidative stress models, DBD models and diabetes-induced urethral dysfunction models. On the contrary, central models represent those resulting from injuries in the spinal cord, brainstem or higher centers, and include lumbar canal stenosis (LCS) models, pelvic nerve injury models, and ventral avulsion models.[11,41]

Ischemic models have been explored for the study of UAB.[9] Animal studies using atherosclerosis-induced chronic ischemia models have suggested that chronic bladder ischemia and repeated ischemia reperfusion during a voiding cycle lead to an increase in oxidative stress, which results in bladder denervation and consequently, in bladder function impairment, thus contributing to UAB development.[38,44]

Moreover, many studies have described the association between diabetes-induced peripheral neuropathy and bladder dysfunction.[45] The mainly model used for DBD is the streptozotocin-induced DM rat model (STZ).[42] Studies using this animal model have demonstrated decreased nerve grown factor levels in the bladder and in L6 to S1 dorsal root ganglia, thus indicating an impaired nerve sensory function. In addition, they also evidenced increased PVR volume, raised bladder capacity, and decreased voiding efficiency, thus evidencing an impaired bladder emptying.[45]

In addition to bladder dysfunction, DM can also result in urethral dysfunction. Diabetes-induced urethral dysfunction models have showed impaired urethral relaxation resulting in an impaired bladder emptying. Moreover, they have also demonstrated an impaired urethral afferent activity leading to the reduction or premature ending of the micturition reflex, and consequently, to a decreased voiding efficiency.[41]

Bladder dysfunction due to LCS has also been recognized as a significant cause of neurogenic UAB.[46] Recently, a rat model of LCS was developed through cauda equina compression by insertion of silicon rubber pieces into the L6 epidural space. It was observed that this compression resulted in deterioration of the afferent and efferent spinal nerves required in the voiding process. Consequently, this animal model revealed a decreased detrusor contractility and an impaired voiding efficiency.[41]

Likewise, traumatic injuries in the conus medullaris and cauda equina portions of the spinal cord commonly result in neurogenic UAB, as well.[47] For this reason, lumbosacral ventral root avulsion (VRA) injury rat models were recently developed to mimic the clinical phenotype of this type of injuries and study neurogenic UAB. Studies using this type of models reported that bilateral VRA injuries result in loss of detrusor contractile capacity, whereas unilateral VRA injuries lead to a partial

impairment of the LUT and a significant decrease of the voiding efficiency.[41,47,48]

In addition, pelvic nerve injury resulting from pelvic surgery has also been associated with UAB development, because it results in afferent and efferent dysfunction of the LUT.[48] Bilateral pelvic nerve crush in adult female rats has been developed as a model to study this event. Cystometric studies using this animal model have reported several results resembling those seen in human studies, including increased bladder capacity and PVR volume, and decreased maximum voiding pressure.[11,49] Furthermore, they also evidenced changed contractility and reduced voiding efficiency, which are suggestive of an impaired bladder function.[49]

Myogenic underactive bladder models

Chronic bladder ischemia may contribute to the development of UAB not only through neurogenic mechanisms, but also through myogenic mechanisms. Therefore, ischemic models also represent myogenic UAB models. Several studies using atherosclerosis-induced chronic ischemia models have suggested that the oxidative stress associated with chronic bladder ischemia generates reactive oxygen species that damage the bladder wall, which results in a decreased muscle contractility and consequently, in the development of UAB.[45]

In addition, apart from ischemic models, there are currently other myogenic UAB models, such as BOO models. So far, several animal studies have been carried out to understand the effects of BOO on bladder detrusor function, including in pig, rat, cat, guinea pig, and rabbit.[20,41] Current animal models typically induce partial BOO by inducing urethra partial obstruction, applying some kind of ligature that obstruct the urethra immediately or gradually.[11] Studies using these models of induced BOO have demonstrated that at an early stage, BOO affects not only the structure but also the physiology of the bladder, leading, in a final state, to impairment of bladder function and potential development of UAB.[12,20] These models showed increased bladder distension as a result of the rise in intravesical pressure. Then, the detrusor muscle underwent compensatory hypertrophy to decrease the intravesical pressure and the outlet pressure resistance associated to BOO. However, after some time, the bladder became unable to properly compensate. At this stage, the bladder contractile capacity decreased, resulting in the development of UAB. In fact, various animal studies have suggested that this decompensated stage is due to cyclic ischemic and reperfusion injury, resulting in myocyte and nerve damage, and consequently, in impaired contractility and denervation, as well. This hypothesis was supported by the use of a color Doppler which showed a significant reduction in the blood flow of the LUT in obstructive models.[12]

DBD model is also a myogenic UAB model, since the etiology of this disease involves both neurogenic and myogenic mechanisms. Cystometric studies demonstrate that STZ-induced diabetic rats reveal time-dependent changes. At an early stage, they undergo compensated changes similarly to detrusor overactivity, and a few weeks later, they enter in a decompensated stage because of the oxidative stress resulting from the associated hyperglycemia, as well as of polyuria. Thus, in this decompensated stage, these animals reproduce some of the features of UAB observed in diabetic patients. They show raised bladder weight, increased PVR volume and voided volume, and reduced voiding efficiency, indicating an impaired bladder emptying.[41]

Limitations of animal models of underactive bladder

The ideal animal model of UAB would be one reflecting the symptoms and etiology of clinical UAB.[41] Current approach of UAB animal modeling focuses on exploring one etiology at a time, which is insufficient and ineffective when applied to study the pathophysiology of a multifactorial condition like UAB.[11]

It is important to consider that exist various structural and functional differences in the bladder, not only between distinct animals, but also between animals and humans. Consequently, animal studies often show significant interspecies variable data, and the obtained findings are not always translatable to humans. The effects of BOO are a specific example of this situation. Contrary to rat models of induced BOO, situations of prolonged BOO do not seem to result in substantial clinical decompensation of detrusor function in humans. In fact, it is this interspecies variability that provides distinct advantages and drawbacks to each animal model of UAB, making them appropriate to explore different characteristics of this condition.[11,41]

However, although current models help to improve UAB understanding, they remain limited.[41] So far, most of the animal studies on DBD) have employed the STZ-induced type 1 DM model, though most of patients have DM type 2.[45] This is a problematic issue, given that there are numerous differences between these 2 types of DM that may result in distinct phenotypes of DBD in both diseases. For this reason, it becomes necessary for future research to focus on studying the pathogenesis of DBD in DM type 2 and developing novel animal models more adequate for this purpose.[45]

Overall, it turns out that the understanding of UAB pathophysiology is still hinder by the absence of proper animal models.[41] Thus, to overcome this problem, more research is needed in the future to enhance animal modeling of UAB, namely by developing animal models that study interactions between the diverse pathologies associated with the onset of this condition.[11,41]

Conclusion

UAB is a complex and multifactorial LUT condition. Even though being common, both in men and women, and responsible for significant impacts in the quality of life of patients, UAB remains poorly understood and with limited and ineffective treatment options available. Although recent advances in UAB research have come to improve our knowledge about the complex pathophysiology of this condition, there are many doubts that remain, namely as regards the translational value of current animal models. Therefore, in the future, more research is required to develop more appropriate animal models that study interactions between the various pathologies involved in the onset of UAB.

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Conflicts of interest

The authors report no conflicts of interest.

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