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Spinu Arsenie Dan
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

Ovidiu Gabriel Bratu
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

Dragos Radu Marcu
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

Adina Elena Stanciu
INSTITUTE OF ONCOLOGY BUCHAREST, DEPARTMENT OF CARCINOGENESIS AND MOLECULAR BIOLOGY, BUCHAREST, ROMANIA

Florentina Gherghiceanu
CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST, ROMANIA

See next page for additional authors

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Authors

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Underactive bladder - an underestimated entity

Spinu Arsenie Dan[1,2], Ovidiu Gabriel Bratu[1,2,3], Dragos Radu Marcu[1,2], Adina Elena Stanciu[4], Florentina Gherghiceanu[1], Florentina Ionita-Radu[5], Simona Bungau[6], Ana Maria Alexandra Stanescu[1], Dan Mischianu[1,2,3]

[1]*Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*
[2]*University Emergency Central Military Hospital, Department of Urology, Bucharest, Romania*
[3]*Academy of Romanian Scientists, Bucharest, Romania*
[4]*Institute of Oncology Bucharest, Department of Carcinogenesis and Molecular Biology, Bucharest, Romania*
[5]*University Emergency Central Military Hospital, Department of Gastroenterology, Bucharest, Romania*
[6]*University of Medicine and Pharmacy, Oradea, Romania*

ABSTRACT

Introduction. The concept of underactive bladder is relatively new. Currently there is no generally accepted definition of this pathology. Diagnosis depends on urodynamic findings, and symptoms are usually rare and intricated with the symptoms of other urinary pathology.

Matherials and methods. This review examines the current literature on underactive bladder regarding pathology, definition, diagnosis, current guidelines, and any further potential medical developments.

Conclusions. Underactive bladder is a poorly understood pathologic condition. Only since 2002 has there been any consensus regarding the definition. The diagnosis relies only on urodynamics; clinical diagnosis is a challenge even for a consultant; and treatment does not seem to alleviate much of the suffering. This disease remains underrecognized and undertreated. More research is needed to identify less invasive diagnosis tools and treatment for this pathology.

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***Corresponding author:**
Dragos Radu Marcu, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
E-mail: marcuradudragos@yahoo.com

Introduction

In 2002, the International Continence Society reviewed the existing data and arrived at a definition for underactive bladder: 'a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span'. However, the definition for this pathology had been evolving over some time. For instance, in 1996 the International Continence Society defined underactive bladder as failure to induce emptying of at least half of the bladder with involuntary recurrent contractions without the evidence of straining, urethral obstruction, and detrusor sphincter dyssynergia. After the 2002 definition was presented (above), in 2010, the society revised the definition as a decrease in detrusor contraction and/or shortening of the contraction time, resulting in an incomplete and/or prolongation of the bladder emptying within the normal time frame [1].

For years, this condition has been overlooked. Its counterpart, the overactive bladder, had received much greater research interest, perhaps due to its more intrusive symptomatology.

The pathology has borne many names: impaired detrusor contractility, bladder failure, bladder decompensation, hypotonic bladder, detrusor areflexia, and detrusor failure and detrusor underactivity, although some authors suggest the last one represents its own category, a point subject to debate [2-4].

The diagnosis for this disease relies mostly on urodynamic findings. The prevalence increases with age and is typically greater in men. Prevalence ranges from 9 to 28% in men under 50 years old and more than 48% in those over 70 years old. In women, the incidence ranges from 12 to 45% [5,6]. Yet, no consensus exists for threshold urodynamic values for disease categorization. Although various papers have proposed different thresholds, no widely accepted guidelines currently exist.

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Discussions

A comprehensive search of PubMed, Scopus, and other databases was conducted using key words like "underactive bladder, detrusor underactivity". Review articles were selected. Several older papers were included for citations and historic interest. Prevalence, etiology, diagnosis, and treatment possibilities were searched. The purpose of this paper is to highlight the cardinal aspects of this pathology.

Etiology

The etiology of this disease is wide and may be separated into five broad categories: idiopathic - young patients with no apparent affections; myogenic - any subvesical obstacle and diabetes, autonomic diabetic neuropathy [7], Parkinson disease, different types of sclerosis, disc hernias [8]; spinal cord injury, spinal dysraphism and stenosis; infectious - HIV, herpes zoster, herpes simplex and neurosyphilis; and last iatrogenic - pelvic surgery, radical prostatectomy, radical hysterectomy [9-11]. In diabetes, chronic hyperglycemic status induces a series of tissues and organ damages. Microvascular involvements in diabetic patients are more common; retinopathy, neuropathy, and chronic kidney disease are the main complications in diabetes. Autonomic diabetic neuropathy develops a series of urological sequelae like erectile dysfunction, retrograde ejaculation, and diabetic bladder dysfunction. More than half of diabetic patients develop diabetic bladder dysfunction, and clinical signs are described as a triad, including a bladder sensation decrease, bladder capacity increase, and imperfect detrusor contractility [12]. Moreover, modifications appear at the urothelium level: decreases in E- cadherin levels and muscarinic receptor 2 and 3 expressions seem to be lower in patients with underactive bladder [13].

The most frequent cause is the neurogenic one; actually disruption of the efferent neural pathways seems to be one of the most frequent types of neural damage. From the pathologic point of view, changes in the ultrastructure of myocytes and gap junctions inhibit detrusor contraction and deposition of collagen between muscle bundle [14,15].

Diagnosis

A proper diagnosis requires some sort of invasive method, specifically urodynamic assessment. The diagnosis can be difficult because of the overlapping symptoms with other pathologies like bladder outlet obstruction, benign prostatic hyperplasia, and overactive bladder. The condition can be deceptive, sometimes presenting with both voiding and storage symptoms. Urgency (63.3%), weak stream (61%), straining to void (57%), and nocturia (48.1%) may all be present, making it difficult to differentiate from other related diseases. In one paper, the authors stressed the importance of pressure flow investigations, as 12,7% of patients with underactive bladder were mistakenly treated with anticholinergics [16].

Patients presenting with overactive bladder and receiving some form of treatment may change at some point in their pathology, and an overstimulated bladder can become hypotonic. Moreover, overactive bladder, bladder outlet obstruction, and underactive bladder can coexist, making it difficult to treat. In diabetes, the first process is bladder hypertrophy with increased contractility, which leads to polyuria. The second stage is linked with hyperglycemic status which leads to the development of toxic metabolites which affect normal bladder function and promote the detrusor muscle dysfunction. In the end stage, both mechanisms will lead to an atonic bladder. Chronic hyperglycemic status induces chronic oxidative stress and releases reactive oxygen species. This partially explains the pathophysiology of diabetic bladder dysfunction, especially damaging neuronal fibers, smooth muscles, and altering urothelial function [17-19]. Recognized clinical risk factors include age, indwelling urinary catheter, diabetes, history of urinary retention, and neurologic conditions [20-26].

Still, many useful tools besides urodynamics are available to help recognize this condition. A thorough anamnesis from the patient is mandatory in order to identify any risk factors for this pathology. A voiding diary is useful to determine the severity of the symptoms; a neurological exam should also be conducted. The Schaefer nomogram or a comparable tool may be used to measure obstruction and detrusor contractility [27].

Efforts are ongoing to identify and standardize different clinical tools that can differentiate this pathology from other lower urinary tract diseases. For example, Gammie et al. compared normal patients with underactive bladder patients: Men with underactive bladder (DU) had statistically higher occurrence of decreased/interrupted stream (56% versus 30%), hesitancy (51% versus 26%), feeling of incomplete bladder emptying (36% versus 22%), palpable bladder (14% versus 1.1%), and absent/decreased sensation (13% versus 3.0%). Women with DU had higher rates of decreased/interrupted stream (29% versus 4.0%), hesitancy (28% versus 9.1%), feeling of incomplete emptying (28% versus 20%), palpable bladder (3.3% versus 1.5%), absent/decreased sensation (4.3%versus 0.8%), enuresis (12% versus 8.4%), and impaired mobility (13% versus 2.8%). On the other hand, when compared to those with bladder outlet obstruction, men with underactive bladder reported higher rates of sexual dysfunction, stress incontinence, palpable bladder, enuresis, training to void, and absence of sensation. Better results included better stream, hesitancy, and urgency [28].

Overlapping their findings with urodynamics should be the next logical step. The symptomatology of this disease

is so undefined that there is need for discrimination tools for all the signs and symptoms [29,30]. For instance, multiple sclerosis can manifest with obstructive symptoms predominantly or diabetes with reduced sensation of bladder fullness due to the diabetic neuropathy.

Urodynamics

Currently, pressure flow urodynamic testing is the only accepted and reliable tool for diagnosing underactive bladder. Even this investigation is controversial, for example, with respect to the maximum normal value of voiding pressure. Moreover, there is no accepted urodynamic definition values for underactive bladder. Several universally accepted parameters can narrow down the list, including a bladder contractility index (BCI) of <100 (PdetQmax + 5Qmax), detrusor pressure at max flow (PdetQmax) of <30mmH2O and a maximum flow rate (Qmax) of <12ml/sec, and a bladder outlet obstruction index (BOOI) (PdetQmax – 2Qmax) of <20 and a Qmax of <12ml/sec [31,32]. Others use the Watts factor, which is an estimate of the power per unit area of the bladder surface that is generated by the detrusor. This measure is not affected by bladder volume and is therefore not influenced by increased outlet resistance. Unfortunately there are no standards for its use, and its complexity makes it a challenge to use [33,34].

Projected isovolumetric pressure - PIP and its derivates: bladder contractility index - BCI and detrusor coeficient - DECO have the advantage of being much easier to use; however, they may overestimate PIP and have less test-retest reliability than measuring isovolumetric pressures directly [35].

Another useful urodynamic investigation is the mechanical occlusion of flow. This test can be controlled by the patient or if needed by the doctor by compressing the urethra. This test tends to underestimate pressure by 20 cc H2O.

Unfortunately, its greatest disadvantage is that it cannot be applied to patients with sphincter weakness or to elderly patients. Compression of the urethra can also be a rather painful procedure. We also mention two other measures, detrusor contraction speed or detrusor velocity, both of which have limited use in general practice [36].

Table 1. A schematic representation of most common urodynamic tests [37].

Methods	**Advantages**	**Disadvantages**
Bladder contractility index BCI = PdetQmax + 5Qmax DU = BCI <100	Easy to use	Not validated in women; cannot measure contraction sustainability
Watts Factor WF = [(pdet + a) (vdet + b) – ab]/2π	Not affected by bladder outlet obstruction (BOO); measures bladder power	Complex formula; impractical to use clinically; cannot measure contraction sustainability; diagnostic thresholds not established
Mechanical flow occlusion Stop test Continuous occlusion test	Measures isovolumetric contraction strength	Cannot be done in those with sphincter weakness or elderly; painful and impractical
Maastricht-Hannover nomogram DU ≤25th percentile	Quantifies relationship between detrusor contractility and BOO	Not validated in women
Urodynamic cut-offs	Easy to use	No accepted normal ranges

Treatment options

Treatment can be classified as behavioral, medical, surgical, and experimental/promising. Behavioral treatment includes time voiding and double voiding, which can reduce the urinary stasis and its subsequent sequelae. Intermittent catheterization or catheterization is one of the last solutions and greatly affects the life quality of the patients and increases the risk of other complications such as infection, urethral stricture, urethroragia, and so on.

Medical treatment, on the other hand, has unfortunately shown little or no success. One of the most used classes of substances are the parasympathomimetics with their main representative bethanechol chloride. This substance is a parasympathomimetic choline carbamate that selectively stimulates muscarinic receptors with little effect on nicotinic receptors. Distigmine bromide, another parasympathomimetic, is an acetylcholinesterase inhibitor that inhibits the acetylcholinesterase enzyme from deactivating acetylcholine, thereby increasing both the

level and duration of action of acetylcholine in neuromuscular junctions. Both of them have been used for many years and both have produced conflicting results.

Barendrecht et al in their review concluded that there is no evidence for using these drugs in the treatment of underactive bladder, taking into account the potential side effects which include nausea, vomiting, diarrhea, gastrointestinal cramps, bronchospasms, salivation, sweating, headache, flushing, visual accommodation defect, and the rare but potentially lethal complication of cardiac arrest. Moreover, this medication showed improvement over the control group only in three of 10 studies, the remaining seven showing no benefit, and one even worsening the symptomatology [38,39].

Alpha blockers represent a widespread medication for bladder outlet obstruction, currently recommended in the European guidelines as first line therapy for this disease. Their effect lies more in the bladder neck where the concentration of alpha receptors is the highest as compared to the overall bladder [40].

The use of colinestherase inhibitors distigmine, pyridostigmine, and neostigmine are efficient neurologic medication and have been supported in the treatment of underactive bladder. For example, Sugaya et al, in relatively recent paper testing distigmine associated with alpha blockers, noticed an improvement in the IPSS score, quality of life scores, and post voiding residue. Still this type of medication has several annoying side effects, including frequent defecation, fecal incontinence, diarrhea, frequent urination, and decrease in physical condition [41].

Prostaglandin E2, a substance derived from cardiac medication, increases detrusor contraction and relaxes the urethra. It is administered intravesically but has no recommendations for sole use. Severa; studies have combined PGE2 with oral bethanecol with promising results, but no general recommendations have as yet followed [42-44].

Acotiamide is an oral agent that regulates the motility of the upper gastrointestinal tract in patients with abdominal symptoms related to hypomotility and delayed gastric emptying. 100 mg dose t.i.d. seems effective for patients with underactive bladder. Sugimoto et al have emphasized this substance as an alternative to distigmine [45].

Surgical treatment consists of a wide variety of procedures and nerve stimulation techniques ranging from sacral electrical stimulation, injections into the external sphincter, trans-urethro resection of the prostate, reduction cystoplasty, latissimus dorsi detrusor myoplasty, transurethral incision of the bladder neck in women, and bladder diverticulectomy.

Some of them, like TUR-P or incision of the bladder neck in women and injections of botulinum toxin into the external sphincter, are surgical procedures meant to relieve the obstruction. Others like reduction cystoplasty, latissimus dorsi myoplasty, and bladder diverticulectomy have the purpose of eliminating the complications of this disease, the aging of the bladder [45,46].

Conclusions

Underactive bladder or any of its synonyms is a poorly understood disease with a very difficult diagnosis. Clinical diagnosis has limited value and positive diagnosis is based only on urodynamics. Even bladder pressure studies have limitations, as normative values are missing. No standardized efficient treatment exists, so therapy tends to be tailored, as some drugs work on some patients, some do not. Medical approach has limited use, surgery can relieve the pressure only for a short time like TUR-P, or it deals with disease complications. Sacral neuromodulation seems for now to be the only real efficient treatment. Future therapies like gene therapy or stem cells therapy show great promise but need to be supported by well-designed empirical studies.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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