TOMMASO CIRO CAMEROTA

# PRIMARY BLADDER NECK OBSTRUCTION:

## A NEW ETIOPATHOGENESIS

HIPPOCRATE

EDITURA VICTOR BABEȘ TIMIȘOARA


**Colecţia: HIPPOCRATE**

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# FOREWORD

Urologic pathology is one of the most exciting in the field of medicine. On the other hand, it is one of the most complicated that frequently implies huge efforts from both medical team and patients. For many years, in urology were taken into account only the so-called ”big problems” of the kidney, urinary bladder and prostate. In last decades urinary pathology has been refined, and besides diseases with a significant organic component, there were characterized a lot of functional entities. The work of Dr Tommaso Ciro Camerota falls in this category and it is an expected and useful publication.

Primary bladder neck obstruction: a new etiopathogenesis is a premiere from many point of views. On one hand, it is the first work of this type in Romania, on the other the author shows a new etiopathogenesis of a very frequent disease in males. The publication is the result of personal clinical practice that was translated into scientific results based on studies done in laboratory. The monograph is characterized by a high degree of originality, but doubled by many important conclusions which are applicable in the clinical practice.

The rationale of this work is particularly based on the symptoms induced by the primary obstruction of the bladder neck. Data about these patients are not easy to collect, and confusing diagnosis is a frequent finding by the advised urologist. In the next step, the analysis and quantification of symptoms seems to be a real challenge, but the author shows some valuable methods to avoid

mistakes. Even so, the author performed a critical analysis of diagnostic procedures and therapeutic solutions.

From these clinical observation and investigation in the lab using GAIT analysis, the author proposes a new etiopathogenic hypothesis, which can have an important effect on therapeutic strategy. This is why Victor Babes Press accepted to print the work of Dr Tommaso Camerota.

**Prof. univ. dr. MARIUS RAICA**

**Timisoara, 2018, May 8**

# ACRONYMS

AUA – American Urological Association

BPH – benign prostatic hyperplasia

EAU – European Association of Urology

EMG – electromyography

EUS – external urethral sphincter

GC – gait cycle

ICIQ – International Consultation on Incontinence Modular Questionnaire

ICUD – International Consultation on Urological Diseases

ICS – International Continence Society

IPSS – International Prostate Symptom Score

IUS – internal urethral sphincter

LUTS – lower urinary tract symptoms

MRI – magnetic resonance imaging

MUI – mixed urinary incontinence

OAB – overactive bladder

PBNO - primary bladder neck obstruction

PVR – post-void residual urine

SUI – stress urinary incontinence

UI – urinary incontinence

UUI – urgency urinary incontinence

# INTRODUCTION

Urinary incontinence and bladder voiding symptoms are extremely frequent in the general population, in both sexes, independently from race and age. Despite quality of life may be extremely impaired, there still exists a stigma which leads patients not to talk about these disorders. Typically, the onset of voiding disorders is slow in time, therefore subjects develop adaptation mechanisms; patients may lose their reference to normality, considering as physiological what in reality is a pathological condition [Abrams, 2013]. Moreover, open source web-based medical information frequently acts as a confounder element. It's becoming more and more frequent to visit informed – but not competent – subjects who arrive to the outpatient clinic with a self-made diagnosis, which is usually the wrong one. In addition, subjects who have no evidence of urological dysfunctions may believe they are sick, while subjects with important objective urological disorders may not have any awareness of it. Mainly for these reasons, it is difficult to collect definitive and reliable epidemiological data on lower urinary tract symptoms and on urinary incontinence in the general population [Burkhard FE, 2016]. When only males are analysed, it becomes even harder to have the right perception of entity and prevalence of voiding disorders; in fact, men are less willing to talk about health problems that in some way affect their intimate sphere. Therefore, the clinical perception and the experience gained in the everyday practice lead to the feeling that these disorders are underestimated, even more in the young male population. In most of the cases – when a correct diagnosis is done,

and an appropriate therapeutic approach is defined – physicians have tools to improve quality of life of these patients, sometimes reaching a complete disappearance of the initial symptoms.

In this book we will review the available epidemiological and physiological data on urinary continence and micturition, with a brief characterization of the possible mechanisms leading to malfunction. Subsequently, we will focus on primary bladder neck obstruction, which is the topic of this publication.

PBNO is an under-investigated niche of pathology characterized by an incomplete relaxation or by an over-activity of the urethral sphincters [Nitti VW, 2005]. This urological disease is quite frequent in the young male. Unfortunately, no adequate and definitive epidemiological data are available. The great majority of published papers on LUTS are in fact focused on men over fifty years-old, who usually present a multifactorial genesis of the disorder. Moreover, etiopathogenetic mechanisms of LUTS have not been adequately investigated in the young male, and too often patients are thought to be affected by chronic abacterial prostatitis, chronic pelvic pain syndrome or psychogenic voiding dysfunction. These three conditions represent diagnoses of exclusion; thus, urologists should be cautious when giving a “label” to a patient. In fact, in the everyday clinical practice it is strong the perception that young male diagnosed with chronic abacterial prostatitis or psychogenic voiding dysfunction may instead have undiagnosed PBNO [Ackerman AL, 2012]. Thus, at first presentation patients usually refer a heavy history of previous treatments and consultations; they exhibit lots of already performed diagnostic procedures and tests, which were frequently negative.

Another limitation in the diagnostic phase regards younger men, who may delay the first presentation because of lack of time

(they are at the beginning of their job activities, and usually have less autonomy in time management), or because of economic costs. The Italian health care system is a cost-sharing-based system, which means that patients have to pay a part of the general economic cost for consultations and procedures. In this scenario, it's not infrequent that young patients decide to postpone their clinical evaluations, underestimating the future impact of the disease. Unfortunately – not only from a health economics point of view, but also from a social perspective – this phenomenon may lead to a more sick and fragile population over time.

For these reasons, we decided to deeply investigate PBNO patients in a multidisciplinary way. We believe that if a traditional urologic evaluation failed in the comprehension of this disorder maybe it was for extra-urological unknown factors, and/or for the inadequacy of the available diagnostic tools. PBNO patients may be extremely disturbed by symptoms, and to date and to the best of our knowledge there are still no recognized effective treatments. In our opinion, this reflects the lack in knowledge of etiopathogenetic mechanisms. Therefore, we decided to give great attention and emphasis to the features of symptoms reported by patients at first presentation, as well as to the onset characteristics of the disorder. We tried to abandon prejudices and preconceptions, and we ask the reader of this publication to do the same.

Based on a preliminary etiological hypothesis that we recently published [Camerota TC, 2016], to a more classical urologic approach we have integrated pain assessment, kinematics, gait analysis, neurophysiological studies and morphological evaluations of pelvis, sacrum and lower back (lumbo-sacral). These comprehensive evaluations allowed us to put a new insight on PBNO, and to define alternative and comprehensive treatments.

We qualitatively and quantitatively analyse multiple variables in patients diagnosed with PBNO. Being an extremely heterogeneous study population, not all the subjects studied underwent the same investigations. In addition, our understanding and expertise on PBNO changed over the years, mostly due to a more comprehensive vision deriving from experience. Therefore, the diagnostic work-flow was adapted over time.

The relationship between musculoskeletal affections and pelvic dysfunctions (such as chronic pelvic pain, or anal incontinence) have been previously described [Hetrick DC, 2003; Salvati EP, 1987; Segura JW, 1979; Altomare DF, 2001], mainly in the female population. In our opinion, the most innovative aspect proposed in this book is the application of this hypothesis to a new study population. To the best of our knowledge, in the male population, the association between postural impairments and voiding symptoms has never been investigated with the approach we are proposing in thispublication.

The first aim of the research was to define whether a correlation between voiding dysfunction and postural or musculoskeletal aspects existed. If so, we were willing to understand if this association was only statistical/epidemiological or if a cause/effect relationship was present. The third aim was to define, if possible, the underlying etiopathogenic mechanism, in order to identify an effective treatment strategy. Finally, aim of this publication was also to analyse the extent to which urological patients needed for rehabilitative medicine and dedicated rehabilitations in the field of Urology. In fact, this topic represents an innovative and challenging subject for the modern medicine, which is increasingly devoted to the patient's needs. More efforts are needed in this field and, more in general, in functional urology, in order to provide better quality of life to our patients.

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*To my newly born son,*

*Filippo*

# ACKNOWLEDGMENTS

First of all, I would like to thank Rector Prof. Univ. Dr. Marius Raica for the generous supervision of the work and for his outstanding scientific support.

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Finally, for sure not for being the last ones, an incredible thank You (!) goes to my Family. Without their silent and continuous support all this would not have been possible.

# I. BACKGROUND

## PHYSIOLOGY OF NORMAL URINARY CONTINENCE

It appears fundamental to briefly review the extremely complex neurological and muscular mechanisms underneath urinary continence and normal voiding function. This field represents the topic of numerous newly published elegant scientific papers which provide, year by year, innovative insights on anatomy, neurobiology, pharmacology and brain imaging. Medical specialists who daily deal with urological diseases involving micturition have the clear perception that the intricate balance which regulates voiding and filling phases has not been completely caught yet. This has relevant implications on the therapeutic side: if the pathological mechanisms of a disease are not completely understood, it would be impossible to plan an effective therapeutic strategy. In this case, usually physicians limit their action to the management of symptoms, which are usually reduced but not completely resolved.

As previously stated, the maintenance of urinary continence and the act of voiding require an integration of multiple complex mechanisms. Neurological circuits originating at various spinal cord levels work in an integrated fashion, each of them releasing a different neurotransmitter. Both in male and female, lower urinary tract is mainly regulated by three efferent pathways [de Groat WC, 2006; Kluck P, 1980; Morrison JF, 2005], as shown in Figure 1 [Fowler CJ, 2008]:

1. sacral parasympathetic nerves. Arising from the S2–S4 spinal segments, these fibres direct to the pelvic plexus – they are also known as pelvic nerves – and provide excitatory control to the detrusor via parasympathetic post-ganglionic nerves.
2. thoracolumbar sympathetic nerves. They originate in the spinal cord at T11-L2, contributing to the formation of the inferior mesenteric plexus and the hypogastric nerve. Their terminal branches provide excitatory control to the bladder neck and to the urethra, while exerting an inhibitory input to the detrusor.
3. sacral somatic nerves. Also known as pudendal nerves, they contain fibres arising from S2-S4 motor-neurons, which are directed to the pelvic floor and to the external urethral sphincter.

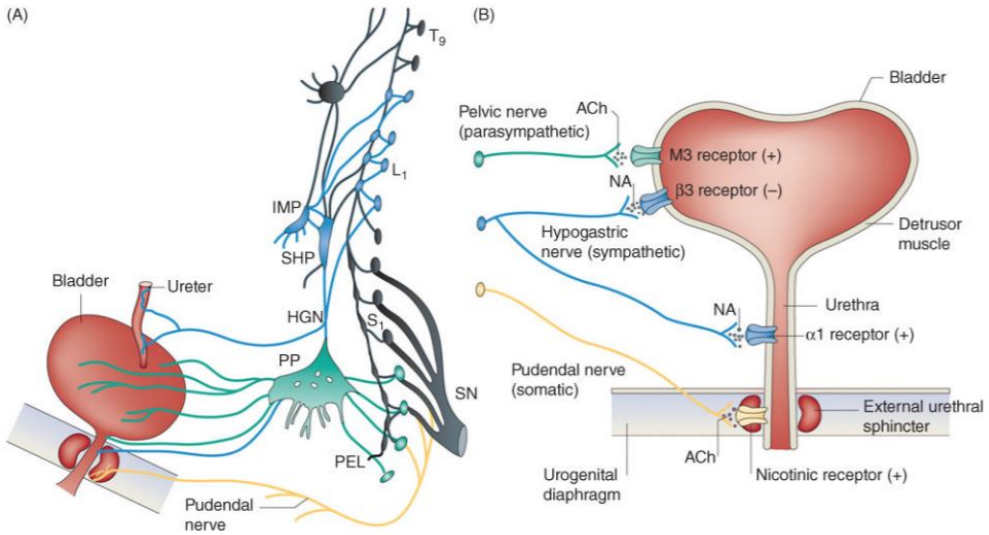


**Figure 1:** (A) efferent pathways to the lower urinary tract. Sympathetic fibres are coloured in blue. Parasympathetic preganglionic fibres are shown in green. Somatic motor nerves are coloured in yellow. (B) Efferent pathways and neurotransmitter mechanisms that regulate the lower urinary tract. Inferior mesenteric plexus (IMP); hypogastric nerve (HGN); pelvic nerves (PEL); pelvic plexus (PP); acetylcholine (ACh); noradrenaline (NA); superior hypogastric plexus (SHP); sciatic nerve (SN) [Fowler CJ, 2008].

Pre-ganglionic efferent neurons – both parasympathetic and sympathetic – release acetylcholine which activates post-ganglionic neurons via nicotinic receptors. Post-ganglionic fibres conversely act via different neurotransmitters: acetylcholine is released by parasympathetic fibres reaching the detrusor, resulting in bladder contraction (voiding phase); noradrenaline is released by sympathetic fibres reaching the urothelium, resulting in bladder relaxation (storage phase). A schematic but clear reproduction of these mechanisms is presented in Figure 1 [Fowler CJ, 2008].

Conversely, afferent pathways from the lower urinary tract to the brain are conveyed by the pelvic, hypogastric, and pudendal nerves. These neural fibres fire to second-order neurons in the lumbosacral spinal cord [de Groat WC, a986; Jänig W, 1986; Yoshimura N, 1997]. Afferent fibres travelling along pelvic nerves carry different information: small myelinated fibres (Aδ) are responsible for bladder wall pressure, while unmyelinated C-fibres convey pain/temperature perception.

On the muscular side, urinary continence in the male – differently than in the female – is controlled by two different sphincters [Hadley HR, 1986]:

- internal urethral sphincter (IUS): located at the bladder neck, mainly containing smooth muscle fibres, regulated by autonomic parasympathetic and sympathetic nerves from the inferior hypogastric plexus;
- external urethral sphincter (EUS): located distally to the prostatic apex, mainly containing striated muscle fibres, it is regulated by the somatic (pudendal nerve) and autonomic (pelvic nerve) nervous system. From a morphological point of

view, EUS includes both the real rhabdosphincter and an adjunctive component known as extrinsic paraurethral skeletal muscle (innervated by parasympathetic branches of the inferior hypogastric plexus) [Abrams P, 2013; Hollabaugh RS Jr, 1998; Gosling JA 1975].

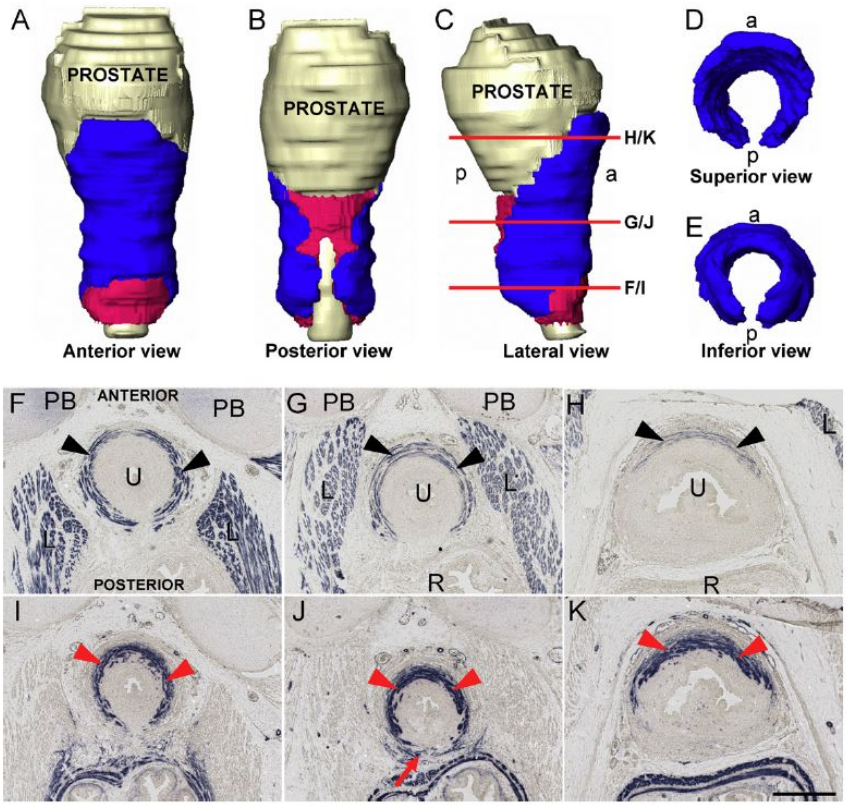


**Figure 2:** EUS (black arrowed) and IUS (red arrowed) in a twelve-weeks of gestation male fetus. 3D reconstruction and immunoistochemical evaluation at different levels show the distribution of striated muscle fibres around the urethra. PB: pubic bone; L: levator ani muscle; R: rectum; U: urethra [Wallner C, 2009].

Autonomic and somatic nerve fibres run together to the urethral sphincter, the first group reaching the smooth muscle fibres at 5 and 7 o'clock, the second group ending at 3 and 9 o'clock.

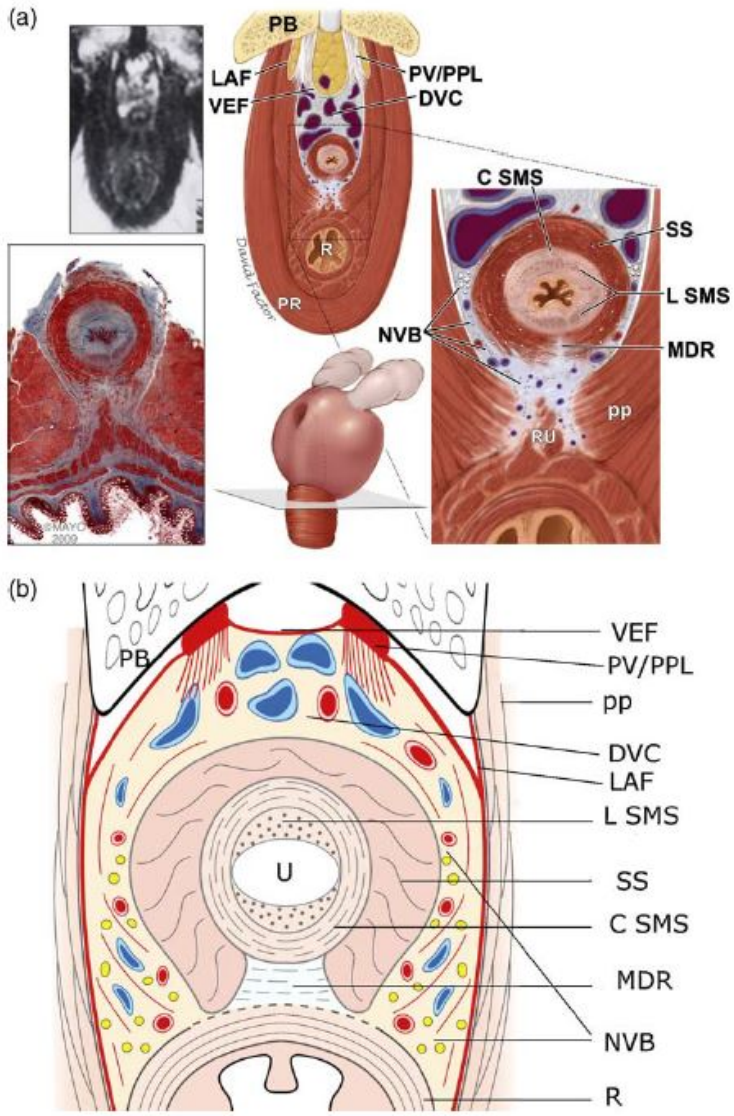


**Figure 3:** axial section of the urethra at the external sphincter level, as appeared on [Waltz J, 2010]. (a) anatomical reconstructions and images elaborated by Mayo Clinic; (b) drawing. DVC: dorsal vascular complex; LAF: levator ani fascia; MDR: median dorsal raphe; NVB: neurovascular bundle; PB: pubic bone; PV/PPL: pubovesical/puboprostatic ligament; PP: puboperinealis muscle; PR: puborectalis muscle; R: rectum; RU: rectourethralis muscle; RR: striated sphincter or rhabdosphincter; CSMS: circular smooth muscle sphincter; LSMS: longitudinal smooth muscle sphincter; U: urethra; VEF: visceral endopelvic fascia.

From a morphologic point of view, the internal sphincter appears to be an extension of the detrusor, which surrounds the bladder neck below the trigone [Ashton-Miller JA, 2007].

The striated muscle fibres are not homogeneously distributed in the EUS, and different patterns are recognizable depending on the location: at the prostatic level they are positioned on the anterior side of the urethra, while in the membranous urethra they appear to be horseshoe-shaped (opened on the dorsal side) crossing the prostatic gland in few points [Karam I, 2005; Sebe P, 2005a]. Elegant anatomical 3D reconstructions and immunohistochemical evaluation are shown in Figure 2 [Wallner C, 2009]. Moreover, as shown in Figure 3, the posterior aspect of the rabdosphincter consists of a tendinous raphe, which is in continuity with the central perineal tendon (caudally) and with the Denonvilliers fascia (cranially). This raphe is considered by many Authors as the fulcrum for rabdosphincter contractions [Burnett AL, 1998; Myers RP, 2000; Strasser H, 2000; Rocco F, 2007].

In normal condition the bladder carries out two different antithetical actions: on one hand the reservoir fills with urine (storage phase), on the other side it empties (voiding phase). This apparently simple on-off activity occurs thanks to the integration of two different functional units of the lower urinary tract: the bladder and the urethral sphincter complex (bladder neck and rabdosphincter). Coordination within the system is guaranteed by neural control at three different levels: peripheral ganglia, spinal cord and brain [Morrison JF, 2005].

During the storage phase, the urethral sphincter complex is contracted preventing urinary leakage, while the bladder progressively relaxes to receive urine. In normal conditions, the increase in bladder volume is accompanied by constant and stable bladder pressures. The control of urethral sphincters is granted by sacral reflexes, also known as guarding reflex, while detrusor is relaxed due to the lack of excitatory inputs from parasympathetic fibres [Fowler CJ, 2006; ID, 2008]. The stimulation of afferent fibres by tension receptors located in the bladder wall determines the activation of sacral parasympathetic efferent fibres and the inhibition of sympathetic and somatic pathways. This represents the beginning of the voiding phase: bladder neck and urethral sphincters relax while the detrusor starts its contraction, the infra-bladder pressure increases, and urine passes. Relaxation of the urethral sphincters depends both on the disappearance of excitatory inputs (adrenergic and somatic) and on the activation of a parasympathetic reflex, which determines the release of nitric oxide (inhibitory neurotransmission).

This neuromuscular integrated system involves not only bladder neck and the urethral sphincters. In fact, the pelvic cavity is inferiorly closed by a sling-shaped muscular structure – the pelvic diaphragm – which supports the abdominal-pelvic viscera together with the uro-genital diaphragm. The pelvic muscular diaphragm is composed by a complex set of structures: the levator ani muscle, the coccygeal muscle and the surrounding connective tissue and fascias. All together, they play a crucial role in the control of urinary (and fecal) continence. Levator ani is the deepest muscle of the anterior pelvis, and attaches on both side to the pubic bone, the ischial spine

and the coccyx. It is made of three different muscle layers: the puborectalis muscle, the pubococcygeus muscle and the ileococcygeous muscle [Ayoub SF, 1979; Wallner C, 2009]. Puborectalis muscle fibres are the most anterior; they attach to the pubic bone, surrounding posteriorly the rectum as a sling. The pubococcygeus and the ileococcygeous muscles attach anteriorly to the pubic bone and posteriorly to the ischial spine. Levator ani also has a muscular component in close contact with the urethral sphincter, which is known as the pubourethral muscle or the levator prostatae. At last, a thin detachment of levator ani muscle, known as the puboperineal muscle, runs between the pubic symphysis and the perineal body.

A voluntary contraction of the puboperineal and of the puborectal muscles determines a forward and upward traction of the urethra, which results in urethral closure and interruption of urinary flow. These muscular structures play a fundamental role in the maintenance of voluntary urinary continence. An impaired control of this complex system may depend on neurological disorders [Abrams P, 2013], on post-surgical damages [Burnett AL, 1998; Myers RP, 2000; Gosling JA, 1982] or on functional diseases [Abrams P, 2013].

Moreover, distally to the urethral sphincter complex – between the anorectal junction and the perineal body – there is a small muscular structure known as rectourethralis muscle, as shown in Figure 3. From a morphological point of view this name appears to be incorrect since this muscle doesn't have any direct contact with the urethra [Brooks JD, 1998; Porzionato A, 2005; Sebe P, 2005b].

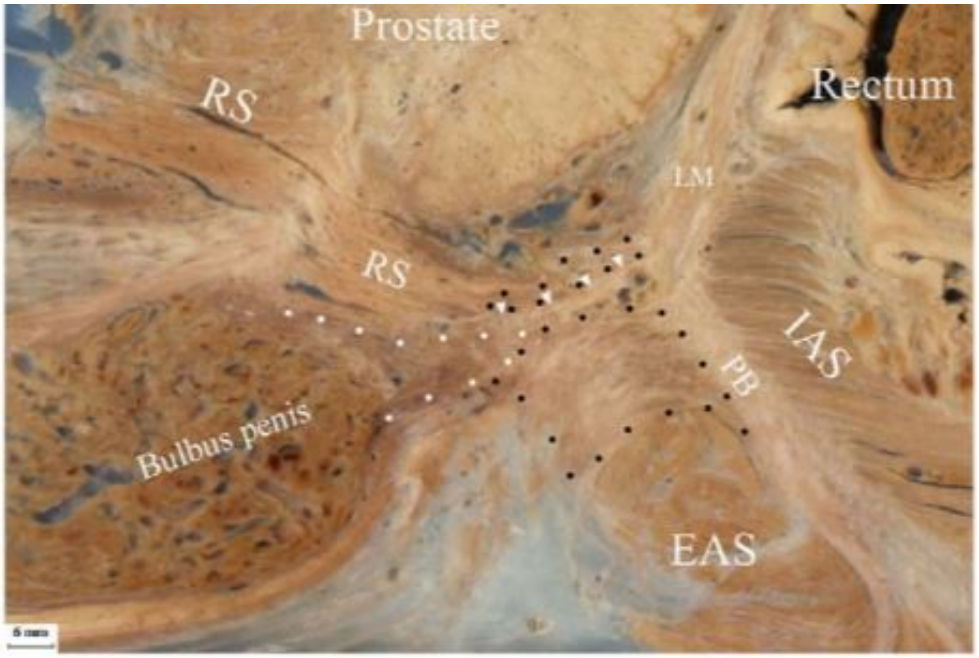


**Figure 4:** sagittal section of the pelvis of a 57-years-old male. White dots: posterior connective tissue of bulbus penis; black dots: deep transverse perineal muscle; white triangles: anterior bundle (rectourethralis muscle). AB: anterior bundle; CG: Cowper's glands; EAS: external anal sphincter; IAS: internal anal sphincter; LM: longitudinal muscle of rectum; RS: rhabdosphincter [Zhai l-D, 2011].

Despite the precise morphology and role of the rectourethralis muscle are still debated, this structure is thought to represent an important stabilizing element to the membranous urethra. An elegant and analytic study demonstrated the anatomical relationship between the rectourethralis muscle and the deep transverse perineal muscle, and between the rectourethralis muscle and the rabdosphincter, as shown in Figure 4 [Zhai l-D, 2011].

These morphological and neuroanatomical considerations represent the basis for an effective urinary continence mechanism in male subjects. The knowledge of these aspects plays a crucial role in

the comprehension of patient reported symptoms at consultation. In fact, the malfunctioning of a mixed nerve (such as the pudendal nerve, for instance) may lead to the development of both efferent (motor) and afferent (sensory) alterations. This inevitably reflects on the complex clinical presentation of PBNO patients. Moreover, a careful characterization of urethral sphincters composition and its activity appears to be fundamental for deeper clinical comprehension in case of malfunctioning. In fact, the striated muscle fibres of the EUS can maintain resting tone and preserve voluntary continence, while the smooth muscles fibres at the bladder neck are responsible for involuntary continence. Interestingly some striated muscle fibres intermix with smooth muscle fibres, merging together and suggesting a coordinated interaction [Karam I, 2005]. An imbalance in this fine control may lead to lower urinary tract symptoms and/or to urinary incontinence.

Lower urinary tract symptoms are possible pathological presentation of an altered micturition. They are traditionally grouped in storage symptoms and voiding symptoms, and represent one of the most common clinical complaints in men [Martin SA, 2011]. LUTS may have an important impact on patient's perceived quality of life [Kupelian V, 2006], and their prevalence increases with age. Lower urinary tract symptoms may be determined by different urological and non-urological conditions, and the same symptomatic presentation may be common to more than a disease.

Lower urinary tract symptoms have historically been thought to be only related to prostatic diseases. However, this initial dogma has been demolished by an enormous scientific production, which

showed that typical determinants of LUTS may be benign prostatic obstruction, foreign bodies, urethral strictures, bladder tumour, distal ureteral stone, urinary tract infection, prostatitis, sleep apnoea, neurogenic bladder dysfunction, and detrusor over-/under-activity.

A classification of lower urinary tract symptoms is listed below:

- storage symptoms as urgency, frequency, urinary incontinence;
- voiding symptoms as hesitancy, terminal dribbling, weak stream, abdominal straining, difficulty in emptying the bladder.

The former represents the endpoint of a malfunctioning in the bladder filling phase, whether the latter accounts for an altered emptying phase.

When evaluating male patients reporting LUTS, voiding symptoms are usually more prevalent, although they are better tolerated than storage symptoms. Thus urgency, frequency and urinary incontinence represent the main driver for medical advice [NIH, 2010; Abrams P, 2002; Speakman MJ, 2004]. Prevalence of disease increases with age, being more predominant in men over 60 years-old.

Urinary incontinence is defined by the International Continence Society as any involuntary loss of urine, and it's considered a storage symptom. Depending on patient's discomfort and referred clinical manifestation, it may be also characterized as [Abrams P, 2002; ID, 2006]:

- urgency urinary incontinence: the leakage is associated or anticipated by an immediate need to void;

- stress urinary incontinence: the leakage is on an involuntary basis, and usually related to exertion or coughing;
- mixed urinary incontinence: the leakage is characterized by symptoms attributable to both the two previous definitions;
- nocturnal enuresis: involuntary loss of urine during sleep.

The epidemiology and prevalence of UI and micturition disorders in men have not been investigated with the same depth and methodicalness as for women. Benign prostatic obstruction and overactive bladder were traditionally accounted for as the two major field of investigation when considering bladder voiding dysfunction in male patients. Moreover, the great majority of scientific publications are addressed to the study of pathogenic mechanism of stress urinary incontinence and urge incontinence following radical prostatectomy for cancer. Voiding disorders unrelated to traditionally recognized urological diseases and/or to surgical procedures have therefore been neglected. For these reasons, there still exist a great lack in comprehension on male voiding dysfunction (bladder and/or bowel). This is even more evident in the younger population: these men may be not considered as patients due to inability of physician/urologist to detect the dysfunction, or due to clinical ignorance. Moreover, functional urological and gastrointestinal disorders are characterized by poor outcomes, which might be referred to psychological aspects. And this can lead to a further underestimation and undertreatment of this medical condition.

When bibliographic research (PubMed/Medline, Web of Science, and Cochrane databases) is performed with the intent of collecting data on UI and bladder voiding dysfunction in males, it

immediately become clear that we do not actually know the real epidemiology of the disease. Data are conflicting, risk factors are partially understood, and – what probably represent the cornerstone – borders among physiology, dysfunction and real pathology are not clear or not already defined. Just to give an example, definitions regarding urinary incontinence may change according to different Scientific Communities or Societies. Moreover, urogenital symptoms are frequently variegated and almost never isolated; bowel and erectile dysfunction may coexist. The possible combinations among all these symptoms are potentially innumerable.

To the best of our knowledge, and despite all the above-mentioned limitations, nowadays it is thought that UI in male have a 1:2 ratio when compared with the female population [Abrams, 2013]. Prevalence of disease range among 1% and 39% in published papers [Boyle P, 2003; Engstrom G, 2003; Bortolotti A, 2000; Smoger SH, 2000; Van Oyen H, 2002; Maral I, 2001; Espuña-Pons M, 2009; McGrother CW, 2004; Malmsten UG, 1997; Finkelstein MM, 2001; Diokno AC, 2007; Irwin DE, 2006; Herschorn A, 2007]. This significant variability it's mostly due to the various definitions adopted to assess and to define what urinary continence or incontinence may be (e.g.: any urine loss in the last year; score on validated incontinence severity index; International Continence Society 2002 definition; etc.). Moreover, the methods used in the survey (e.g.: self-administered questionnaire; postal questionnaire; personal interview; telephonic interview; etc.) may influence interpretation of data and results.

A systematic review on 69 studies reported a prevalence of UI ranging from 4.81% up to 32.17%. Independently from the given definition of UI, a steady increase in prevalence with age was confirmed by all the Authors [Shamliyan TA, 2009]. The distribution

among different types of UI in men may change accordingly with age. For the purposes of this publication, it is interesting to notice that young patients have the highest rate of urge urinary incontinence. Conversely, the older is the patient the higher is the probability of mixed types of incontinence (e.g.: stress urinary incontinence plus urge urinary incontinence). In Table 1 we summarized the results of the most relevant published epidemiological researches.

| Citation | Population | Age group | UUI (%) | SUI (%) | MUI (%) | Others (%) |
|---|---|---|---|---|---|---|
| **Irwin 2006** | n.19.165 | >=18y | 22.2 | 11.1 | 11.1 | 53.7 |
| **Herschorn 2007** | n.482 | >=18y | 58 | 27 | 15 | - |
| **Shamliyan 2009** | Meta-analysis of 126 publications | 19-44y | 68.2 | 16.3 | 15.5 | - |
| | | 45-65y | 59.3 | 28.9 | 11.7 | - |
| | | >65y | 54.2 | 8 | 17.9 | - |
| | | >80y | 65.9 | 0 | 34.1 | - |
| **Diokno 2007** | n.21.590 | >=18y | 44.6 | 24.5 | 18.8 | 12.1 |
| | | 18-34y | 30 | 38.1 | 14.8 | 17.1 |
| | | 35-44y | 35.4 | 35.8 | 12.6 | 16.2 |
| | | 45-54y | 38.9 | 30.8 | 16.5 | 13.8 |
| | | 55-64y | 46.8 | 19.3 | 21 | 13 |
| | | 65-74y | 53.8 | 16.7 | 22.6 | 6.9 |
| | | >75y | 56.3 | 13.2 | 22.4 | 8.1 |

**Table 1:** prevalence and characterization of different kinds of urinary incontinence in male population.

As previously described, the normal control of urinary continence and of voiding is based on an extremely complex system. Not only it depends on neurological and muscular aspects, but it also requires the integration of endocrinological elements, psychological aspects, individual habits, mechanical and “hydraulic” mechanisms. Due to this complex articulation, too many are the possible levels of interference; and this is maybe why older men – usually affected by multiple diseases as, for example, diabetes, neurological disorders, BPH, impairment in activity of daily living, etc. – present with mixed urinary incontinence.

# PRIMARY BLADDER NECK OBSTRUCTION

Primary bladder neck obstruction represents an inappropriate or inadequate relaxation of the bladder neck during micturition; consequently, this urological condition results in an obstructed urinary flow in the absence of any clear anatomic obstruction (e.g.: benign prostatic enlargement in men or genitourinary (e.g.: increased striated sphincter activity in both sex, benign prostatic enlargement in men or genitourinary prolapse in women). It was previously proposed an association with an external urethral sphincter hypercontraction [Nitti VW, 2005], but no conclusive data are available.

Firstly described more than eighty years ago [Marion G, 1933], it was called in many different ways along time: bladder neck dyssynergia, dysfunctional bladder neck, Marion's disease, and PBNO. The latter is the actually most used definition, which takes the lack of a precise known pathogenic mechanism into account.

For a long time it has been considered a rare condition. The poor epidemiological data initially available reflect the lack of sufficient urological expertise and the inadequate understanding of the underlying cause(s). On the contrary, recent evidences support the belief that PBNO could represent the most common cause of lower urinary tract symptoms in young male patients (under 50 years-old) with no other urological obstructive causes [Ackerman AL, 2012]. In fact, it has been identified in up to 47-54% of male patients aged 18-45 years with chronic voiding dysfunction symptoms [Kaplan SA, 1996; Nitti VW, 2002], and even in up to 15% of children with persistent voiding symptoms not responsive to conventional

treatments [Grafstein NH, 2005]. Nevertheless, the real incidence and prevalence of PBNO are not completely known.

As already stated, to date a definitive aetiology leading to PBNO has not been recognized [Nitti VW, 2005], thus various etiopathogenetic hypotheses have been presented. Among these, the most reliable scientific theories presented are:

- an incomplete dissolution of mesenchymal tissue or an excessive amount of connective tissue [Leadbetter GW, 1959];
- an abnormal morphologic arrangement of the detrusor/trigonal musculature [Turner-Warwick R, 1973];
- a sympathetic nervous system dysfunction determining an altered control at the bladder neck [Awad SA, 1976; Woodside JR, 1980];
- structural changes at the bladder neck such as fibrous narrowing or hyperplasia [Nitti VW, 2005].

At first presentation, patients usually report a wide variety of symptoms, both attributable to storage and voiding phase. In the available literature, a prevalence of storage symptoms – mainly urinary urgency, in up to 79% of PBNO patients – have been described [Yang SS, 2002; Grafstein NH, 2005; Glassberg KI, 2010]. Moreover, urological symptoms are nonspecific, and are common to many other urological diseases.

Differential diagnosis includes urinary infections, acute bacterial prostatitis, urinary stones, benign prostatic obstruction [Vuichoud C, 2015], cicatricial urethral strictures [Bayne DB, 2017] and detrusor-external sphincter neurological dyssynergia [Stoffel JT,

2016]. These conditions are usually excluded with initial clinical and diagnostic evaluations such as urinalysis, uroflowmetry with post-void residual urine and abdominal ultrasound.

Although it has been also described in female patients, PBNO appears to be predominant in the male population. In the available literature, only few females were recognized as to be affected by PBNO: 21 women were described in a total of three publications [Diokno AC, 1984; Axelrod SL, 1987, Kessler TM, 2006], while whereas a 4.6% incidence was identified in a urodynamic evaluation of a large cohort of women referring LUTS [Nitti VW, 1999]. Interestingly, interstitial cystitis/bladder pain syndrome – a urological disease more typical in female population – presents epidemiology, clinical features and characteristics of symptoms [Mullis C, 2015] for many aspects similar to those of primary bladder neck in the male population.

Usually presenting with vague symptoms – and having a physical examination with no abnormal findings – PBNO patients are frequently considered anxious or affected by other diseases such as type III prostatitis, prostatodynia or chronic pelvic pain syndrome. A previous publication showed that primary bladder neck obstruction was diagnosed in 23 young and middle-aged men previously thought to be affected by prostatitis, neurogenic bladder or psychogenic voiding dysfunction [Norlen LJ, 1986]. Unfortunately, this initial diagnostic error leads the patient to receive a “label”, and frequently many years are needed before a correct diagnosis is done. In some publications, it has been reported that the mean time to diagnosis is 6.7 years [Trockman BA, 1996].

Due to the lack of relevant physical findings, the diagnosis is primary based on clinical suspicion and on exclusion of other diseases. Despite the prostate has historically been thought to be the major (only) responsible for the genesis of LUTS, this dogma was challenged by the evidence of no prostatic affection in PBNO male patients. Moreover, it is infrequent for patients with benign prostatic obstruction to present with associated pain, whilst this may be extremely recurrent in primary bladder neck obstruction. The morbidity of PBNO may be relevant, and often leads to poor quality of life for patients and sometimes also for their relatives.

The diagnostic workflow to reach a diagnosis of PBNO usually requires the administration of patient reported outcome measures, the collection and the interpretation of bladder diaries, a deep medical history collection and an accurate physical examination. Based on the results of these evaluations, a subsequent panel of diagnostic tests may be activated. The most important urological procedures are uroflowmetry (showing plateau and/or interrupted urinary flow), post-void residual urine (with no clear presence of a recurrent pattern) and urethrocystoscopy (for endoscopic confirmation of the diagnostic suspicion). Previous publications reported also the extensive use of urodynamic tests and voiding cystourethrography in men with a long history of urological complains [Turner Warwick R, 1973]. It was also proposed a classification based on urodynamic results, which recognize three possible types: a high vesical pressure with low voiding flow, a normal vesical pressure with low voiding flow, and a delayed opening of the bladder neck [Nitti VW, 2002].

If a correct diagnose of PBNO is done, patients may be treated with:

- watchful waiting, usually reserved for patients who are not strongly bothered by their symptoms, and who do not present signs of decompensation of the upper and lower urinary tracts (such as hydronephrosis or bladder diverticula);
- behavioural therapies as, for example, controlled hydration, use of laxatives, time voiding, modification of urinary habits;
- physiotherapy, as pelvic floor muscle exercises;
- visual or EMG-based biofeedback treatments. Unfortunately, these cures have not been proven effective as the bladder neck function is under the control of the autonomic system;
- pharmacotherapy. Alpha-adrenergic blockers (such as terazosin 2-5 mg/day, doxazosin 2-4 mg/day, prazosin 2 mg twice daily) are the most commonly used medications to treat PBNO, although there are no evidences of long-term efficacy. It was also shown that adherence to treatment is low in these patients, as only 24% of them continued therapies for longer than one year [Nitti VW, 2002]. Other proposed medications are antispastic or muscle relaxants – baclofen, among others – that unfortunately may present important and limiting side effects such as confusion, nausea, weakness, constipation (which may worsen, if already associated with PBNO), muscle or joint pain. Some Authors also proposed combination therapies, but no specific data are available;
- endoscopic bladder neck incision (unilateral or bilateral). This treatment is certainly highly effective when pre- and post-

operative maximum flow rate are compared [Norlen LJ, 1986; Kaplan SA, 1994]. Unfortunately, it is not risk free: retrograde ejaculation represents the more relevant and not tolerated possible post-operative side effect, as frequently young PBNO male patients desire paternity. Depending on the method of post-operative evaluation, it was described in 27%-100% of patients receiving this procedure [Norlen LJ, 1986]; its frequency is lower in unilateral incisions [Kaplan SA, 1996; Webster GD, 1980], but in all the cases it's irreversible;

- endoscopic injection of botulinum toxin A. Some Authors proposed the injection of 100 units diluted in 10mL normal saline in ten sites (two each at the trigone, bladder neck, proximal prostatic urethra, distal prostatic urethra, external urethral sphincter) [Chen JL, 2009], while other Authors proposed the injection of 200 units diluted in 4mL normal saline in four sites at the bladder neck (3-6-9-12 o'clock, 1ml/site) [Sacco E, 2013]. Although it may appear a fascinating therapy, to date the patients treated are very few, sites of injection are not reproducible, and no arm-control study has been performed in PBNO patients. Moreover, the effects of botulinum toxin A are short in time (up to 6-10 months), thus repeated treatments are required for long-term effectiveness. This is positive in case of no effect or side effects from botulinum administration, but it may condition a poor compliance to therapy in those patients with an initial good clinical response [Chen JL, 2009];

- sacral neuromodulation has been also proposed, but few data are available thus it is still considered experimental and anecdotal [Goldman HB, 2006].

More frequently, PBNO patients do not receive any specific therapy as no definitive cause of disease has been identified up to now and no in-depth comprehension has been possible.

Otherwise, if a correct diagnosis is missed, these patients may receive improper therapies depending on the diagnosis hypothesized by the clinician:

- drugs (alpha-lytic or 5-alpha reductase inhibitors) or disobstructive surgery in case of BPH;
- prolonged antibiotic and anti-inflammatory therapies in case of chronic nonbacterial prostatitis;
- prolonged analgesic therapies or electrostimulation in case of chronic pelvic pain syndrome;
- intermittent clean self-catheterization and pudendal nerve block or, exceptionally, transurethral sphincterotomy or placement of urethral stents in case of neurogenic bladder or detrusor-sphincter dyssynergia.

In other words, primary bladder neck obstruction appears to be a urological black box: we do not know too much of it, thus it may represent a green field for new researches.

# II. SCIENTIFIC APPROACH AND REASERCH

## 1. CLINICAL AND INSTRUMENTAL EVALUATIONS

From November 2013 to October 2017 all the patients presented for outpatient urological consultation to the same urologist (Tommaso Ciro Camerota) were prospectively evaluated. Among more than 6.000 outpatient evaluations and diagnostic procedures individually performed, 71 male subjects reporting chronic voiding dysfunction were diagnosed with PBNO. Patients with neurological disorders, diabetes mellitus, previous major injuries, lower limbs or back surgery were excluded from the study. All the subjects included in this doctoral research underwent a comprehensive medical evaluation described in the following section. None of the patients received treatments for PBNO before the study.

### UROLOGICAL EVALUATION

All the 71 patients affected by PBNO were identified and clinically evaluated by Tommaso Ciro Camerota (Urologist); all the urological diagnostic procedures (non-invasive and invasive) were performed by the same physician.

To date, it does not exist a standardized protocol for the diagnosis of PBNO. According to the current International Guidelines for non-neurogenic LUTS [Irani J, 2003; Speakman MJ, 2004; Novara

G, 2006; McVary KT, 2011; Bosch J, 2013; Gratzke C, 2015; NIH, 2017] and urinary incontinence [Lucas MG, 2012; Abrams P, 2013; Burkhard FE, 2016], the diagnostic workup adopted in this research consisted of.

a. deep investigation of general and medical history. Many factors (drugs, other diseases, previous surgery, lifestyle, etc.) may influence the normal urinary and faecal continence.

b. careful characterization of the reported symptoms. Frequently patients focus only on a predominant symptom, and have no complete perception of the complexity of the micturition discomfort or of other eventually associated disorders (bowel or penile sensitivity alteration, pelvic/perineal pain or dysesthesia). The more accurate is the initial investigation, the more probable is the precise identification of the pathogenic mechanism underneath symptoms, and the setting of a correct therapy.

c. accurate physical examination for the evaluation of abdominal, flank and pelvic objectivity. Due to the young age of patients enrolled, digital rectal examination was performed only in case of long-term presence of symptoms (more than two years), in case of reported fever (to exclude prostatitis) or in case of suspected benign prostatic enlargement. Neurological examination was always performed, principally focusing on reflexes and trigger-points; a more in-depth discussion of these aspects will be carried out in a following section on pain assessment.

d. urinalysis (physical, chemical, and microscopic evaluation of urine sediment), to search for leucocyte esterase or nitrite, pyuria, glycosuria, ketonuria or proteinuria. Frequently LUTS may be elicited by infections, diabetes or stones. This non-invasive inexpensive test may help in defining the subsequent diagnostic workflow, which may vary from patient to patient. In case of haematuria or history of heavy-smoking, urine cytology on three samples were asked to exclude the presence of a possible – although infrequent in young subjects – transitional carcinoma of the bladder/upper urinary tract.

e. administration of validated questionnaires (patient reported outcome measures). These may be of some help when the reported symptoms are vague, when the physician suspects an unreliable or uncompliant patient, or to monitor disease course during therapy. The most used questionnaires were International Prostatic Symptoms Score to define LUTS [Barry MJ, 1992] and International Consultation on Incontinence Modular Questionnaire to exclude urinary leakage [Avery K, 2004; Coyne K, 2010].

f. collection of diaries (frequency-volume chart), which consist in written reports of data regarding bladder and bowel functioning during normal patient's life. Voiding diaries are semi-objective measurement of the frequency and severity of LUTS. An accurate and precise filling of these forms can provide more information to the urologist than too many investigations asked without a precise focus. They are useful in a better qualification of patient's reported symptoms, and in the identification of

eventual discrepancies. Moreover, in many cases they represent a good support to the definition of the underlying pathological mechanism of storage LUTS. Voiding diaries were asked for at least three consecutive (if possible) days, while bowel diaries were asked for 10-14 consecutive days. Figure 5 and figure 6 respectively show the bladder and the faecal diaries adopted in this research.

g. blood tests were not routinely asked, and were only reserved to patients with a suspicious of possible renal impairment (serum creatinine, urea) or prostatitis (total PSA, reactive C protein, procalcitonin).

h. uroflowmetry with post-void residual urine, a non-invasive diagnostic investigation used to measure the flow and force of urine stream during micturition. Uroflowmetry is performed by urinating into a special funnel connected to a measurement device that calculates the voided volume and the rate of flow voided per second. At the end of micturition, post-void residual urine (amount of urine that eventually remains in the bladder after voiding) is measured by bladder ultrasound or by catheterization. Depending on the morphology of the curve, on the flow rate (average and maximum) and on PVR, this investigation may suggest the diagnosis and influence the following diagnostic workflow [Abrams P, 2003; van Waalwijk van Doorn E, 2000; Rosier PFWM, 2013a]. In case of doubtful or noncoherent results, it is advisable to repeat the exam at minimum twice.

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**Bladder diary**

Keeping a daily bladder diary will help You and Your healthcare professional to better understand Your voiding symptoms. See instructions on the back of this page.

| Day | time | quantity | accidental leaks | symptoms |
|---|---|---|---|---|
| | A | B | C | D |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
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**Figure 5:** bladder diary template. In a 24 hours diary, patients were asked to fill a line of the form every time they void. A. time; B. voided volume (mL), assessed by passing urine into a measuring jug; C. eventual presence of accidental urinary leakage (drops or flow; small, medium, large amount); D. eventual symptoms (e.g. urgency, feeling of incomplete voiding, none, etc).

i. first level imaging, as abdominal ultrasound to exclude the presence of urinary stones, hydroureteronephrosis, transitional carcinoma of the bladder, etc.

j. outpatient flexible urethrocystoscopy, in order to exclude the presence of cicatricial urethral strictures or prostatic hyperplasia causing compression/occlusion to the urethra. A 16Ch flexible cystoscope from Karl Storz was used to study all the patients.

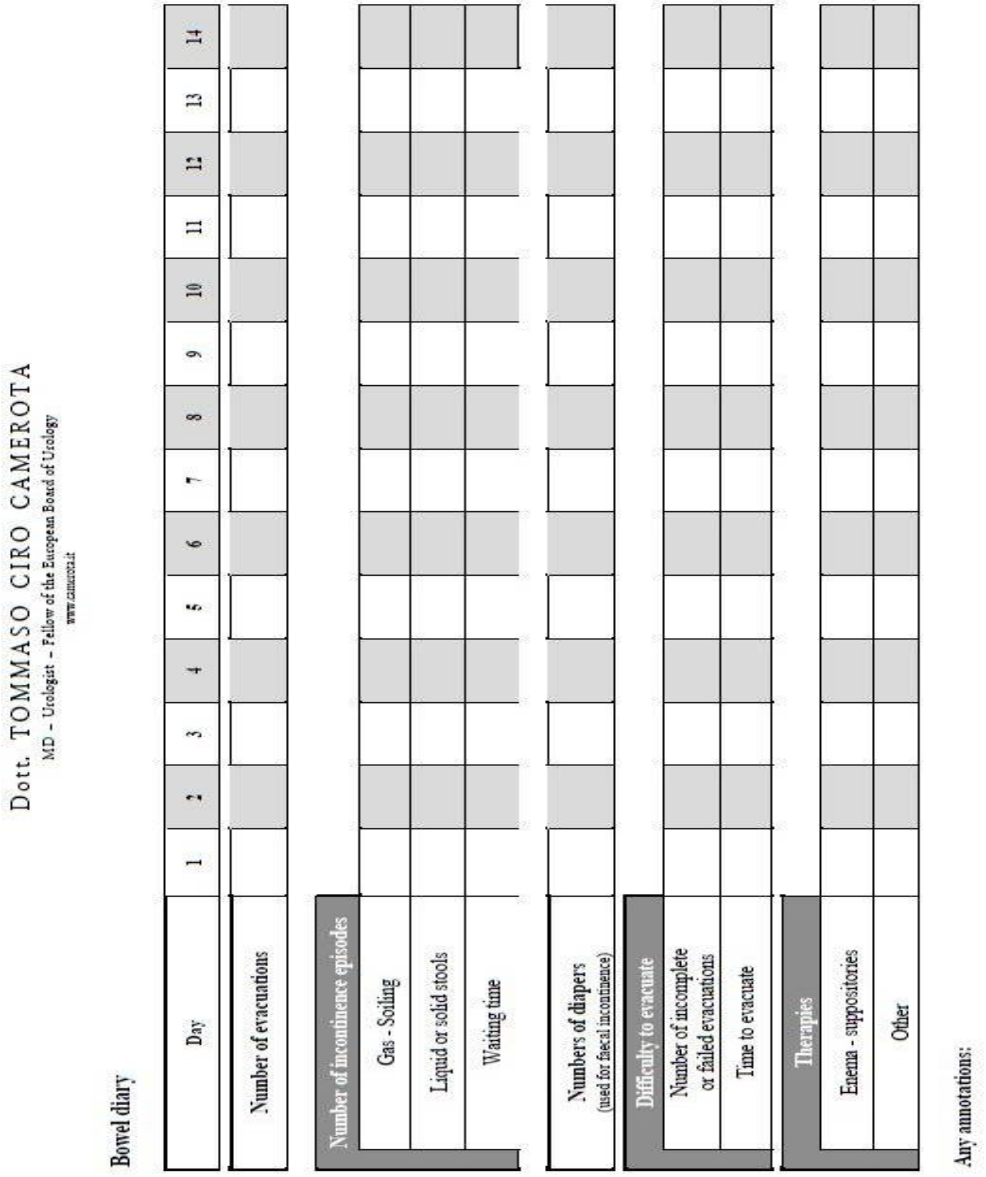



**Figure 6:** bowel diary template. Columns represent different days (of a 14 possible, per each form). Records concern bowel movements and faecal consistency, with the time of day and circumstances (e.g. strain, feeling of incomplete evacuation, etc), and eventual assumption of fibre supplements or laxatives.

k. second level imaging: according to patient's history and complains (mostly severity and duration of urological and pain symptoms), we asked for a full spine X-ray – on a single image, to reduce any alterations due to the overlap of multiple scans – in two standard projections (antero-posterior, latero-lateral), a pelvic-perineal MRI, and/or a lumbosacral spine MRI.

l. neurophysiological testing such as concentric needle EMG, sacral reflex responses to electrical stimulation of penile nerves, and pudendal nerve latency.

The abovementioned procedures and tests are internationally standardized, thus only a brief general description was carried out. In the following section we extensively describe pain assessment, which is usually underestimated by urologists. On the contrary, in our experience it represents a crucial complementary element for a correct clinical and diagnostic assessment.

## PAIN ASSESSMENT

Pain is a subjective, multidimensional experience and clinical assessment must proceeds by subsequent clinical steps to understand its origin and its pathobiology [Dansie EJ, 2013; Hague M, 2014]. The first step was a complete neurological examination to rule out any peripheral or central nervous system damage [Haanpää M, 2011]. Motor evaluation and strength against resistance were always performed. Peripheral sensory fibers (Aβ, Aδ and C fibers) were clinically evaluated and pathological finding were registered. If an

allodynic area was found, a differentiation between peripheral mechanisms (impulse multiplications), nociceptors hyperactivity or central sensitization was conducted to guide subsequent treatments.

A postural assessment was integrated at the end of the pain evaluation. Correct posture minimizes stress on muscles, bones, and joints while incorrect posture places abnormal stress on these structures. The more posture deviates from the correct position, the greater the stress placed on the structures that work to maintain it. Postural defects can be used to identify alterations in muscle and ligament length.

In this systematic evaluation a psychophysiological assessment was also included; in fact, psychological factors are influencing physical responses to pain and may provide behavioral feedback strategies for coping.

Referred pain is pain perceived at a location other than the site of the painful stimulus/origin. It is the result of medullar convergence of the interconnecting sensory nerves. Provocative tests are commonly used methods to exclude referred pain and to precisely assess pain. During a provocative test, the physician performs a specific physical maneuver in an attempt to recreate the pain reported by patient. A positive result means the test was able to recreate pain. A combination of many evocative tests is commonly carry out because a single test is not enough sensitive and specific to confirm a diagnosis. For example, if a sacroiliac joint dysfunction was suspected the following tests were used to obtain a clinical diagnosis [Broadhurst NA, 1998]: distraction test (tensile forces on the anterior aspect of the joint), thigh thrust (anteroposterior shear stress), FABER

(Flexion, Abduction, External Rotation - tensile force on the anterior aspect), compression test (compression force), Gaenslen's test (torsion stress).

Pain medicine assessment of eventual pelvic pain was focused on lumbar muscles and vertebra, hip, coccyx, pubic bones, pelvic muscles (clinical examination and pelvic MRI images), iliohypogastric, ilioinguinal, genitofemoral and pudendal nerves and was associated with a deep urological and coloproctological evaluation. Moreover, potential sources of pain due to nerve entrapments were assessed both clinically and by ultrasound examination looking for hyperechoic fibrotic areas or neuromas.

After a deep clinical examination performed as described above, only a diagnostic suspicion can be made; therefore, anesthetic blocks represent the subsequent step for a correct diagnosis of the involved tissue. For this purpose, a small amount of local anesthetic was injected under ultrasound guide to interrupt pain transmission in a specific tissue, and patients were asked to quantify and qualify their perception of pain modification. The anesthetic block test was considered positive if a >50% pain reduction was obtained. In case of persistent high clinical suspicion but no response to the anesthetic block (possible previous false negative block), the physician reevaluated the patient's symptoms and repeated the same procedure; otherwise, a different anatomic area was considered in case of lower clinical suspicion in the initial area. These steps were used to reveal the pain generator and to guide the subsequent therapeutic treatments (local anesthetic plus steroid injections).

Ultrasound was always used for interventional pain management as it allows the identification of soft tissues, vessels and nerves; moreover, it allows the visualization of the injected anesthetic in a real-time fashion [Narouze, 2011].

## GAIT ANALYSIS EVALUATIONS

Gait Analysis is defined as the analysis of walking patterns of humans. A major application area is in the clinical decision-making and treatment processes for neuro- musculoskeletal diseases, among others such as security clearance systems and human identification [Simon SR, 2004]. In this context, three-dimensional instrumented clinical gait analysis provides comprehensive data on normal and pathological gait, which are useful in clinical practice and scientific purposes because they provide objective information about joint motions (kinematics), time-distance variables (spatio-temporal data), and joint moments and powers (kinetics). Clinical gait analysis is an important method to obtain crucial information to determine the level of functional limitation due to pathology and for its follow-up evaluation over time [Cimolin V, 2014]. The obtained results represent objective gait characterization of a given individual. Gait analysis therefore may represent an objective standardized evaluation of an initial clinical observation.

**PARTICIPANTS**

Recruitment started in 2014, and was proposed to ten consecutive newly diagnosed PBNO patients. Among the 71 male patients enrolled in our research, a subset of seven subjects (named P1 to P7) were recruited for a gait evaluation. Being part of the research population, none of these patients subjectively perceived motor or postural impairments nor presented abnormal reflexes at neurological evaluations. In these subjects, PBNO was diagnosed with bladder diary, uroflowmetry and urethrocystoscopy (to exclude urethral strictures or benign prostatic obstruction). Exclusion criteria were previous history of orthopaedic surgery or neurological disorders. Mean age was 39.6 ± 7.1 years; mean height and mass were 177.4 ± 6.4 cm and 76.1 ± 7.5 kg, respectively; mean body mass index was 24.14 ± 0.76 kg/m$^2$. Images of a full spine X-ray in two projections were collected from all the patients. Severity and time of onset of the urological symptoms for each patient are summarized in Table 2.

Data from an existent laboratory database were used as control. Control group consisted in 40 normal-weighted, physically healthy subjects (29.1±4.7 years; body mass index: 24.5±1.12 kg/m$^2$; walking speed: 1.10±0.07 m/s). Data were recorded with the same rules and under the same conditions as for patients diagnosed with PBNO. Exclusion criteria for controls were known previous or actual urological, neurological, proctologic or orthopaedic disorders, chronic pelvic pain, and previous surgery. Mean body mass index in the control group was 24.5 ± 1.12 kg/m$^2$.

Patients' urological symptoms collected at anamnesis.

| | Participant | | | | | | |
|---|---|---|---|---|---|---|---|
| | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
| Age (years) | 31 | 40 | 29 | 42 | 37 | 38 | 51 |
| Duration of symptoms (in months) | 2 | 144 | 12 | 28 | 10 | 1 | 15 |
| *Storage symptoms* | | | | | | | |
| Frequency | X | X | X | X | – | X | X |
| Urgency | – | X | – | X | – | – | – |
| Incontinence | – | X | – | – | – | – | – |
| Painful bladder sensation | X | – | – | – | X | – | – |
| Nocturia | – | X | – | – | – | – | – |
| *Voiding symptoms* | | | | | | | |
| Intermittent stream | – | X | – | – | X | X | – |
| Hesitancy | – | X | – | X | – | X | X |
| Straining | – | X | – | X | – | X | X |
| Terminal dribble | X | X | X | X | X | X | – |
| *Post-void symptoms* | | | | | | | |
| Feeling of incomplete voiding | – | X | – | X | X | X | X |
| Post-micturition dribble | X | X | – | X | – | X | – |

**Table 2:** quality, severity and time of onset of the urological symptoms complained at the anamnestic interview by the seven patients with PBNO enrolled in the gait analysis study.

## PROCEDURES

Research activities and data collection were performed at the Department of Biomedical Sciences for Health of the University of Milan, in the LAM Laboratory (Laboratorio di Analisi del Movimento). Gait trials were recorded, analysed and interpreted by a multidisciplinary research group coordinated by Prof. Chiarella Sforza (Full Professor of Human Anatomy at the University of Milan), and consisting of Tommaso Ciro Camerota (Urologist), Matteo Zago (postdoctoral fellow in Clinical and Sports Biomechanics at Politecnico di Milano, Italy), Daniela Ciprandi (Ph.D. candidate at the University of Milan), Stefano Pisu (student in Sports Sciences at the University of Milan). The Local Ethics Committee approved the procedures and all participants provided informed written consent.

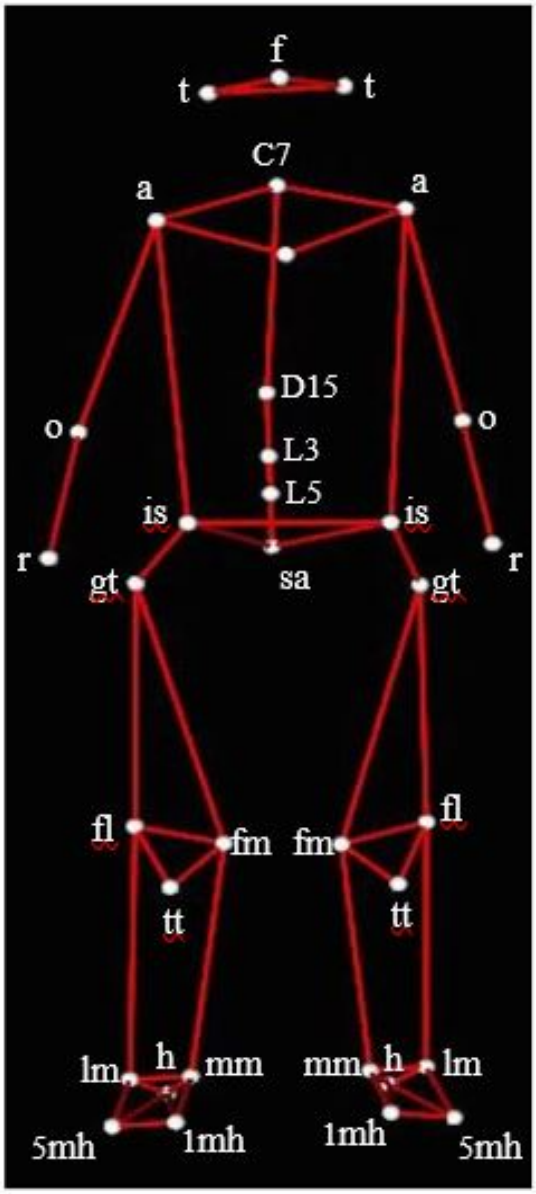



**Figure 7:** schematic reconstruction of the 35 markers positioning in the kinematic model adopted in our research. f: forehead; C7; st: sternum: sa: sacrum; D15; L3; L5; t: tragi; a: acromia; o: olecranons; rs: radius styloid processes; is: posterosuperior iliac spines; gt: greater trochanters; fl: femoral lateral epicondyles; fm: femoral medial epicondyles; tt: tibial tuberosities; mm: medial malleoli; lm: lateral malleoli; 1mh: first metatarsal heads; 5mh: fifth metatarsal heads; h: heels.

A 9-cameras three-dimensional optoelectronic motion capture system (BTS Spa, Milan, Italy) was used to record (at a sampling frequency of 60 Hz) participants' gait. Subjects were asked to walk ten times through an oval circuit. Of each trial, the two or three central steps were retained, in order to analyse only patterns recorded under optimal conditions. Therefore, we were able to collect 20-30 steps for each patient. Participants wore only minimal clothing (underwears, socks), were barefooted and asked to walk their self-selected, comfortable speed. Thirty-five passive markers were fixed by the same operator on the subjects' skin in the following anatomical landmarks: forehead (f), C7, sternum (st), sacrum (sa), D15, L3, L5, tragi (t), acromia (a), olecranons (o), radius styloid processes (rs), posterosuperior iliac spines (is), greater trochanters (gt), femoral lateral (fl) and medial (fm) epicondyles, tibial tuberosities (tt), medial (mm) and lateral (lm) malleoli, first (1mh) and fifth (5mh) metatarsal heads, heels (h). Figure 7 shows a schematic representation of the landmarks positioning.

**DATA ANALYSIS**

Data analysis returned a comprehensive report for each subject, consisting of joint angular kinematics and spatiotemporal parameters. The analysed variables were:

- *ankle dorsi flexion-plantar flexion*, which measures kinematic behaviour of the ankle on the sagittal plane;
- *ankle eversion-inversion*, which measures kinematic behaviour of the ankle on the horizontal plane (eversion and inversion);

- *knee flexion-extension*, which measures kinematic behaviour of the knee on the sagittal plane;
- *hip flexion-extension*, which measures kinematic behaviour of the hip on the sagittal plane;
- *hip abduction-adduction*, which measures kinematic behaviour of the hip on the frontal plane;
- *hip rotation*, which measures kinematic behaviour of the hip on the horizontal plane;
- *pelvis tilt*, which measures the kinematic behaviour of the pelvis on the sagittal plane (anteversion and retroversion);
- *pelvis obliquity*, which measures the kinematic behaviour of the pelvis on the frontal plane (left-side and right-side movements);
- *pelvis rotation*, which measures the kinematic behaviour of the pelvis on the horizontal plane (clockwise and anticlockwise rotation);
- *trunk flexion/extension*, which measures the kinematic behaviour of the trunk on the sagittal plane (front and back inclination);
- *trunk bending*, which measures the kinematic behaviour of the trunk on the frontal plane (left-side and right-side movements);
- *trunk rotation*, which measures the kinematic behaviour of the trunk on the horizontal plane (clockwise and anticlockwise rotation);
- *step length* (average);
- *cadence*, expressed as steps per minute;

- *variability*, expressed as coefficient of variation (SD/mean) of step length and stance (%);
- *coordination repeatability*;
- *stance & swing*, expressed as the % duration of stance and swing phases across the gait cycle;
- *joints RoM* (joints angular Range of Motion), which is maximum minus minimum value across the gait cycle.

Each variable was graphically represented in order to provide an immediate visual insight of the trend of each individual variable when compared to the same one in the control group. Reconstructions were performed according to the following standardized rules:

- results from the control group were always represented in grey (confidence interval);
- if the evaluated variable is a single one (e.g.: trunk or pelvis), results were coloured green;
- if the analysed variable is a bilateral one, as in the case of the lower limbs, results were coloured in blue for the right side and in red for the left side.

An example is shown in Figure 8.

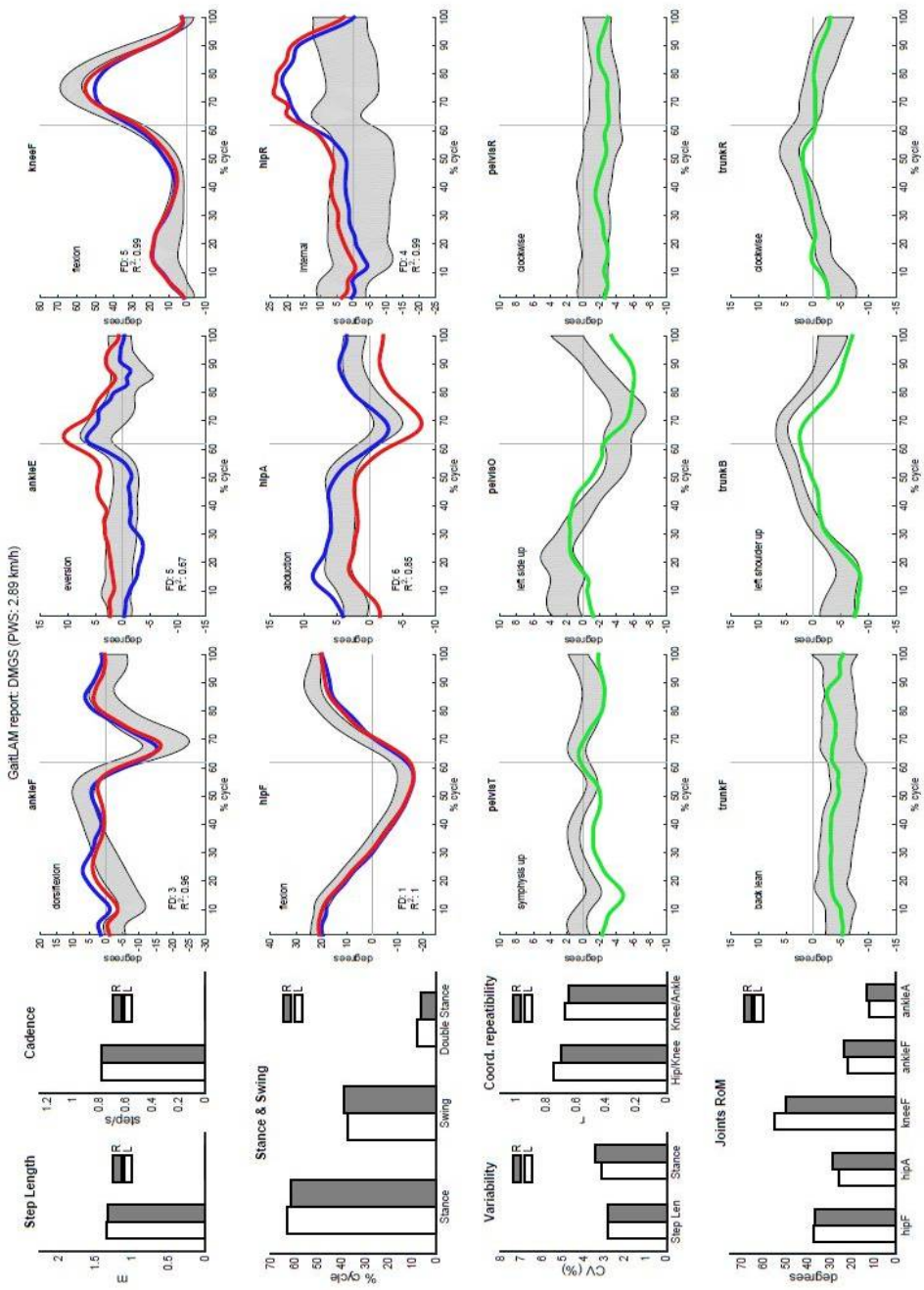



**Figure 8:** example of an analytical report obtained with gait analysis. The results presented refer to P2.

In order to assess the overall similarity of patient's gait patterns with respect to the normative database, a multivariate statistical approach based on a Principal Component model was adopted. In short, the objective was to get synthetic index that brings into one the number of gait variables (of a possible 18) that are similar to the normal pattern, providing an immediate numeric interpretation of the results. The higher is the score, the lower is the discordance among the patient's gait and the control group.

Data reduction and statistical analysis used for the research are extensively described in our published paper [Zago M/Camerota TC, 2017], and will not be discussed in this publication.

## MAGNETIC RESONANCE IMAGING

Multiplanar pelvic and perineal MRI was performed on a total of 22/71 patients, with 1.5 tesla (Siemens) and 3 tesla (General Electric) MRI scanners respectively in 7 and 14 patients. All the images were reviewed by the same physicians: Dante Broglia, who is both radiologist and orthopaedic, and Tommaso Ciro Camerota (Urologist).

# 2. INNOVATIVE SCIENTIFIC EVIDENCES

## DESCRIPTIVE STATISTICS OF THE STUDY POPULATION

In the period between November 2013 and October 2017 a total of 71 male patients were diagnosed with PBNO by the same urologist (Tommaso Ciro Camerota). Median age at diagnosis was 41 years (interquartile range: 33.25 - 47.75), while median symptoms duration until diagnosis was 12 months (interquartile range: 6.5 - 25.5). Almost all the subjects (97%; n.69/71) reported the presence of a physiological urinary stimulus, with no differences in perception (increased or decreased). Seventy percent of the patients (n.51/71) were afflicted by both irritative and obstructive voiding symptoms; 13% of the subjects (n.9/71) exclusively reported obstructive urinary symptoms, while 3 patients (4%) had only irritative symptoms. No statistically significant differences were found when evaluating the incidence of irritative versus obstructive symptoms ($p=0.21$ at Chi-square test). Characteristics and severity of urological symptoms in our study population are summarized in Table 3.

| *Storage symptoms* | *n.* | *%* | *Voiding symptoms* | *n.* | *%* | *Post-void symptoms* | *n.* | *%* |
|---|---|---|---|---|---|---|---|---|
| Frequency | 49 | 69 | Straining | 46 | 65 | Feeling incomplete voiding | 41 | 58 |
| Urgency | 38 | 54 | Intermittent stream | 29 | 41 | Post-micturition dribble | 26 | 37 |
| Nycturia | 14 | 20 | Hesitancy | 28 | 39 | | | |
| Incontinence | 5 | 7 | | | | | | |

| *Combination of symptoms* | *n.* | *%* | | *n.* | *%* |
|---|---|---|---|---|---|
| Frequency + Urgency | 34 | 48 | Urgency + Feeling incomplete voiding | 25 | 35 |
| Frequency + Feeling incomplete voiding | 34 | 48 | Urgency + Straining | 24 | 34 |
| Frequency + Straining | 33 | 46 | Frequency + Intermittent stream | 21 | 30 |
| Straining + Feeling incomplete voiding | 33 | 46 | Urgency + Intermittent stream | 17 | 24 |

**Table 3:** distribution of urological symptoms as reported by PBNO patients at first presentation (total n=71). For each symptom/combination of symptoms both the number of patients and the percentage among our study population are indicated.

Voiding symptoms were not isolated in our study population. The concomitant presence of other pelvic or perineal disorders was relevant, and was observed with the following distribution:

- defecation pattern: 7% (n.5/71) of the patients reported alternating bowel habits, 8% (n.6/71) colitis, 18% (n.13/71) constipation, while 66% (n.47/71) reported normal defecatory habits;
- erectile function: 25% of the patients (n.18/71) reported a variable degree of impairment in erectile function. Among these subjects, 94% (n.17/18) had erectile attainment disorders while 100% had erectile maintenance disorders;
- ejaculation: 35% of the patients (n.25/71) reported a variable degree of ejaculation disorders as reduced ejaculated volume, perineal pain or cramp, urethral discomfort or tingling sensation

at the tip of the penis immediately after ejaculation. Only 20% of the entire study population (n.14/71) reported the concurrency between ejaculation and erectile function disorders;

- pain (pelvic, perineal, pubic, lumbosacral, sacroiliac or inguinal) was reported by 76% of the subjects (n.54/71).

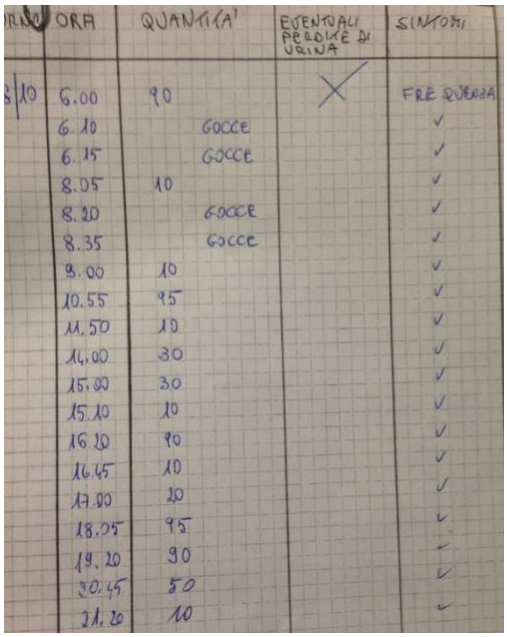
No relevant comorbidities were found except for actual or previously operated inguinal (unilateral or bilateral) and/or umbilical hernias, which were overall observed in 44% of the patients (n.32/71).

**PATIENT REPORTED OUTCOME MEASURES**

Forty-four subjects (62% of the entire study population) correctly filled and delivered frequency-volume charts and bowel diaries. Unfortunately, it was not possible to obtain both the diaries from all the subjects enrolled in this doctoral research, mainly due to patient's noncompliance.

The collected bladder diaries shown the following micturition pattern (an example is presented in Figure 9):

- increased voiding frequency per 24 hours, mostly during daytime hours;
- preserved total voided volume per 24 hours, as expected;
- significant reduction of the volume emptied per single void (median 172.5, interquartile range 141.3 – 287.8), with a minimum volume of 10 mL.



| ORA | QUANTITA' | EVENTUALI PERDITE DI URINA | SINTOMI |
|---|---|---|---|
| 6.00 | 90 | X | FRE QUENZA |
| 6.10 | GOCCE | | ✓ |
| 6.15 | GOCCE | | ✓ |
| 8.05 | 10 | | ✓ |
| 8.20 | GOCCE | | ✓ |
| 8.35 | GOCCE | | ✓ |
| 9.00 | 10 | | ✓ |
| 10.55 | 95 | | ✓ |
| 11.50 | 10 | | ✓ |
| 14.00 | 30 | | ✓ |
| 15.00 | 30 | | ✓ |
| 15.10 | 10 | | ✓ |
| 16.10 | 90 | | ✓ |
| 16.45 | 10 | | ✓ |
| 17.00 | 20 | | ✓ |
| 18.05 | 95 | | ✓ |
| 19.20 | 90 | | ✓ |
| 20.45 | 50 | | ✓ |
| 21.20 | 10 | | ✓ |

**Figure 9:** example of a voiding diary filled by a patient with PBNO, and collected during the diagnostic phase of the research. Noteworthy are the increased number of micturition per day, and the reduced volume emptied per single void.

**UROLOGICAL INVESTIGATIONS**

Both uroflowmetry with PVR and endoscopy (urethrocystoscopy) were performed by Tommaso Ciro Camerota in all the 71 patients enrolled in this research. PVR was always measured by bladder ultrasound.

The following uroflowmetric characteristics were identified in our cohort of patients at diagnosis:

- mean peak flow rate was 12.89 ± 4.58 mL/s (range, 4-21 mL/s);
- mean average flow rate was 6.22 ± 2.98 mL/s (range, 3–15 mL/s);
- mean voided volume was 304.2 mL (range 95 - 780mL)
- mean post-void residual urine was 72.72 ± 53.32 mL (range, 0-180 mL);
- 28% (n. 20/71) patients presented intermittent (complete or incomplete) stream 69% (n. 49/71) subjects had plateau flow,

while 82% (n. 58/71) of the study population had urinary straining. The great majority of patients presented a combination of more than one of these flow characteristics.

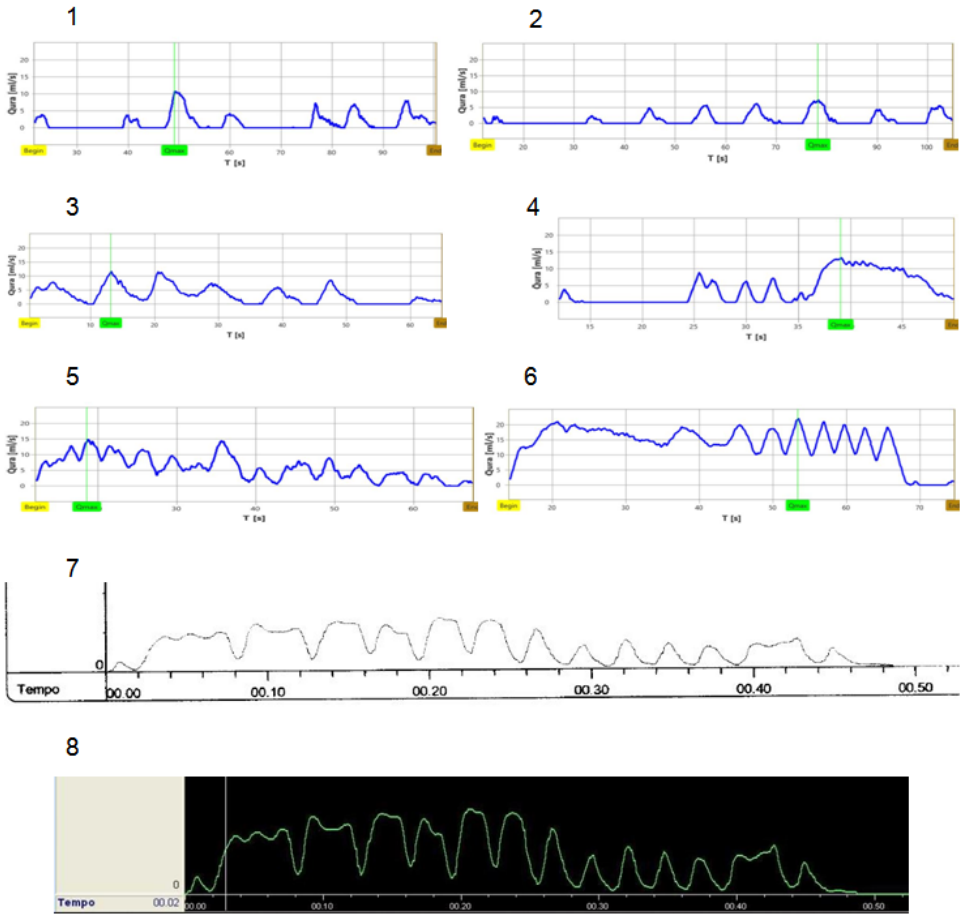



**Figure 10:** uroflowmetries collected from eight different PBNO patients enrolled in our research. Intermittent stream was observed in 28% of the study population, and was either complete (as in cases n. 1, 2, 3, 4) or incomplete (as in cases n. 5, 6, 7, 8). In the former case urinary flow reaches the 0 pressure, while in latter case abdominal straining induces a relaxation of the urethral sphincter complex with a consequent flow resumption.

Figure 10 and Figure 11 show some of the more representative uroflowmetric patterns observed during our research.

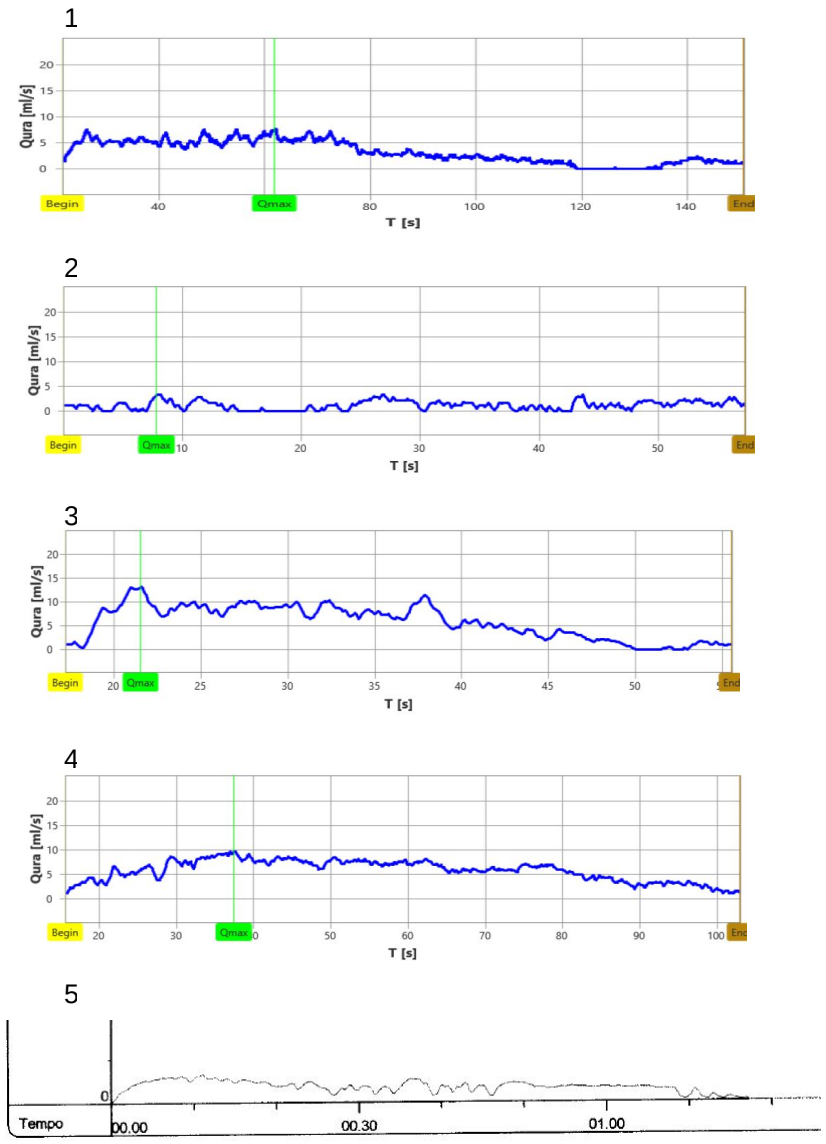



**Figure 11:** uroflowmetries collected from five different PBNO patients enrolled in our research. Examples of plateau flows, which may also be prolonged, are shown. This pattern could also suggest the presence of a urethral stricture; thus, to define a proper diagnosis, it is mandatory to perform a cystoscopy.

At urethrocystoscopy, all the 71 PBNO patients presented small non-obstructive prostate, tight external urethral sphincter, and contracted bladder neck. Furthermore, it was of frequent observation the presence of bladder wall trabeculations or initial bladder diverticula resulting from high pressures generated by the detrusor muscle to overcome sphincters' resistance. This endoscopic procedure allowed to exclude the presence of cicatricial urethral strictures, benign prostatic obstruction, transitional cell carcinoma of the bladder or vesical stones. Few examples of bladder neck contracture and urethral sphincters' endoscopic appearance in our study population are shown respectively in Figure 12 and in Figure 13.

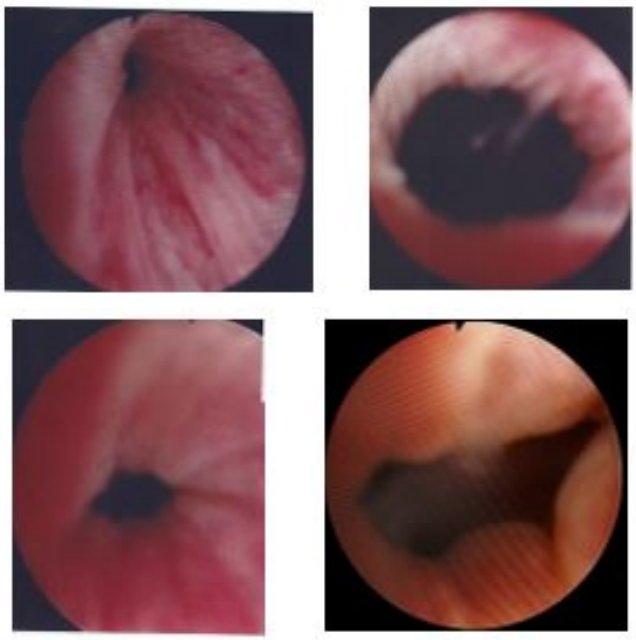


**Figure 12:** endoscopic appearance at the bladder neck in four of the 71 patients diagnosed with PBNO and enrolled in the present research.

**SPINE X-RAY**

A full spine X-ray on a single image was obtained in 49% (n. 35/71) patients enrolled in this doctoral research. None of the patients showed a physiologic appearance. When compared to normalcy, the major pathological findings were:

- lumbar hyperlordosis;
- horizontalization of the sacrum and increase of the sacral slope:
- hooked coccyx;
- anterior tilt of the pelvis;
- lower limb length discrepancy;
- variable degrees of scoliosis;
- obturator foramina asymmetry;
- partial or complete congenital sacralization of L5 vertebrae;
- mild anterolisthesis of L5 on S1;
- radiographic L5-S1 disk height reduction;
- cervical spine rectification.

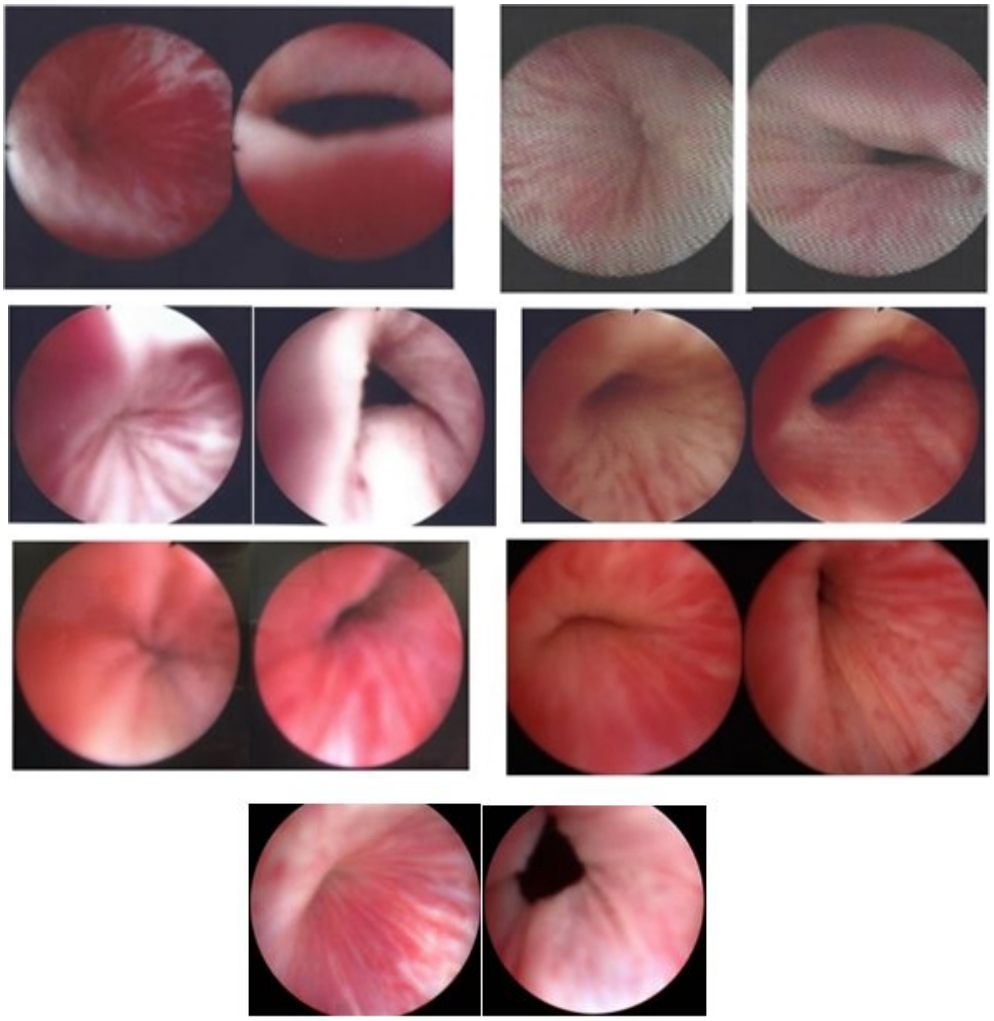


**Figure 13:** endoscopic appearance of both the urethral sphincters in seven of the 71 patients diagnosed with PBNO and enrolled in the present research. Each pair of images refers to the same subject; the external urethral sphincter is always shown on the left side, while the internal urethral sphincter (bladder neck) is shown on the right side. All the procedures were performed on awake patients on an outpatient basis.

In our study population, PBNO patients frequently had more than one of above mentioned conditions. In Figure 14 an extract of significant images is presented.

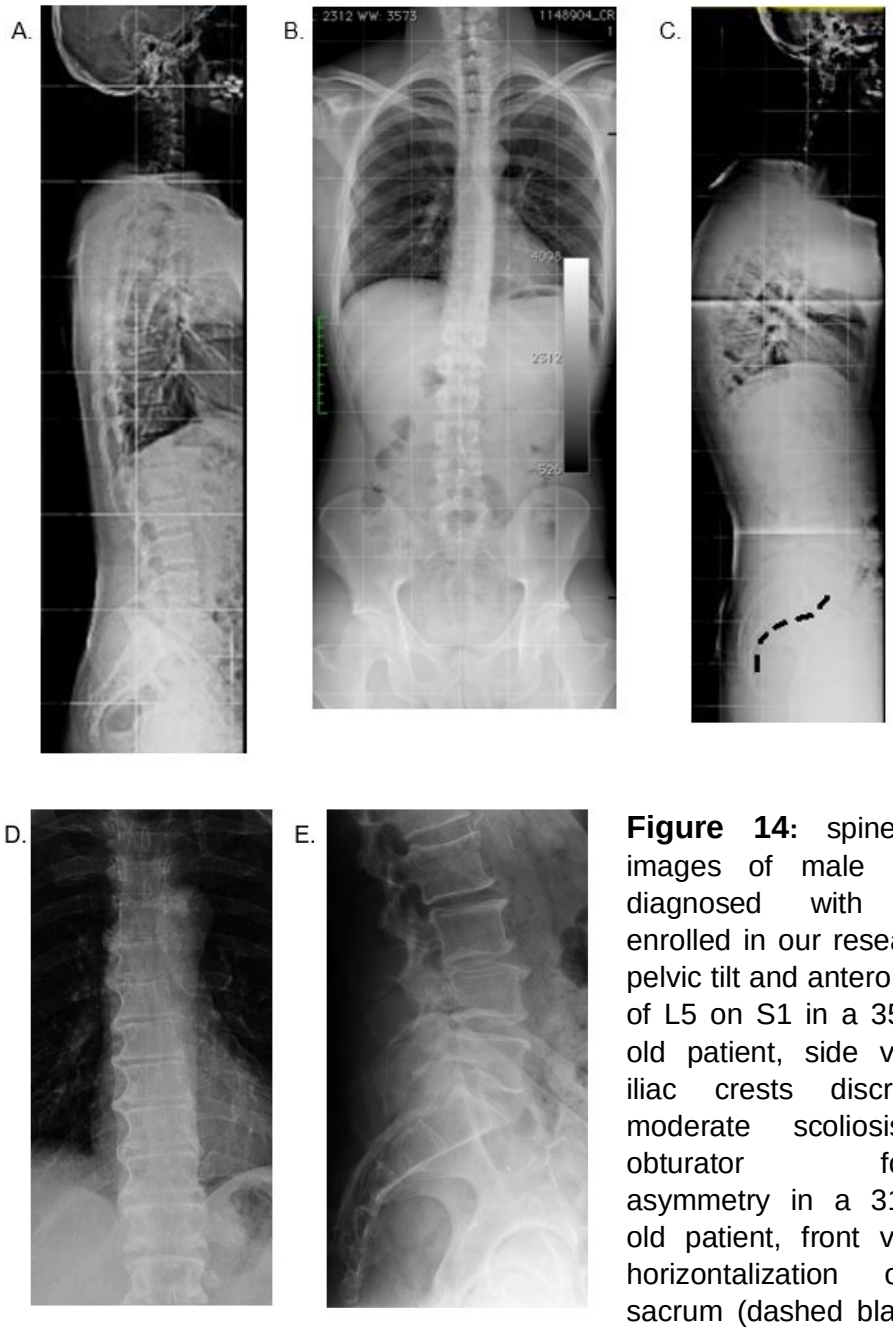



**Figure 14:** spine X-ray images of male patients diagnosed with PBNO enrolled in our research. A. pelvic tilt and anterolisthesis of L5 on S1 in a 35-years-old patient, side view. B. iliac crests discrepancy, moderate scoliosis and obturator foramina asymmetry in a 31-years-old patient, front view. C. horizontalization of the sacrum (dashed black line) and cervical spine rectification in a 36-years-old patient, side view. D. bamboo-like spine of a 56-years-old patient, front view. E. horizontalization of the sacrum and increase of the sacral slope in a 48-years-old patient, side view.

**MRI**

MRI of the pelvis and of the perineum was obtained in 31% (n. 22/71) of the patients enrolled in this research. Axial, coronal, and sagittal 1.5T or 3T (depending on the scanner) images were obtained in all the subjects. The adopted sequences were T2 fast relaxation fast spin echo (FRFSE), T1 short-tau inversion recovery (STIR), liver imaging with volume acceleration-flexible (LAVA-Flex), T1 fast spoiled gradient echo (FSPGR), T1 fast spin echo (FSE) and T1 turbo spin echo (TSE).

No relevant differences in diagnostic quality were noticed between the two MRI scanners. The different muscular components of the pelvic floor were clearly identifiable, and the trophic tone of the muscles was appreciable and measurable. A comparison on the symmetry or on the laterality of muscular hypertonicity or hypotonicity was performed.

None of the MRI revealed normal findings. Hypertonicity or hypertrophy of pelvic floor muscles were identified in all the 22 subjects. Various and heterogeneous anomalies (skeletal or muscular) were identified, and are listed below:

- external urethral muscle thickening;
- hooked coccyx or its anterior angulation;
- sacroiliac joint sclerosis or sacroiliitis;
- posterior disc protrusion al L3-L4-L5-S1;
- sacrotuberous ligament thickening;
- piriformis muscle contraction or hypertrophy;
- pelvic upslip or rotation;
- obturator internus muscle tendinitis;

- gluteus minimus muscle atrophy;
- pubo-rectal muscle hypertrophy;
- rectus-adductor syndrome;
- femoroacetabolar impingement;
- levator ani muscle thickening;
- sacralization or hemisacralization of L5, which is a fusion of the first sacral vertebra and the 5$^{th}$ lumbar vertebra;
- anterolisthesis L4-L5;
- Alcock canal inflammation;
- biceps femoris tendinopathy;
- falciform ligament inflammation;
- sclerosis or erosion at the pubic symphysis.

The most significant MRI findings identified in our study population are shown in Figures 15, 16, 17, 18 and 27.

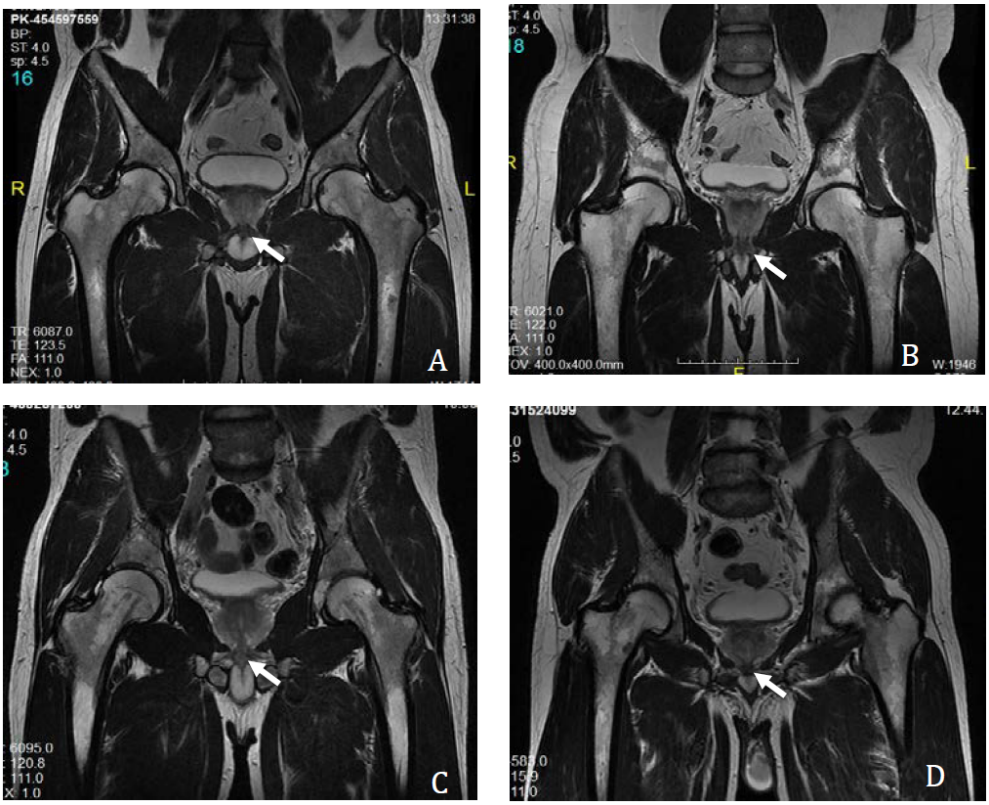



**Figure 15:** MRI images collected in four male patients diagnosed with PBNO enrolled in our research, frontal views. External urethral muscle thickening (white arrows) in a 44-years-old patient (A), 56-years-old patient (B), 37-years-old patient (C) and 57-years-old patient (D).

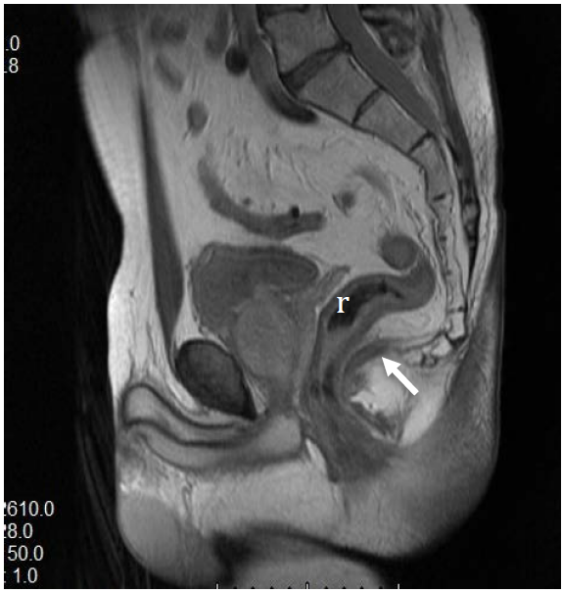



**Figure 16:** MRI of a 57-years-old male patient diagnosed with PBNO, sagittal view. Rectum (r) is lifted up due to anococcygeus muscles hypertonicity (white arrow).

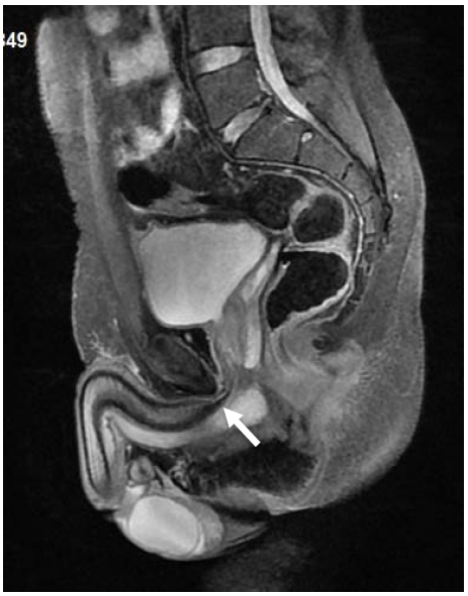


**Figure 17:** MRI of a 35-years-old male patient diagnosed with PBNO, sagittal view. hypertonicity of deep transverse perineal muscle (white arrow) determine a compression on membranous urethra.

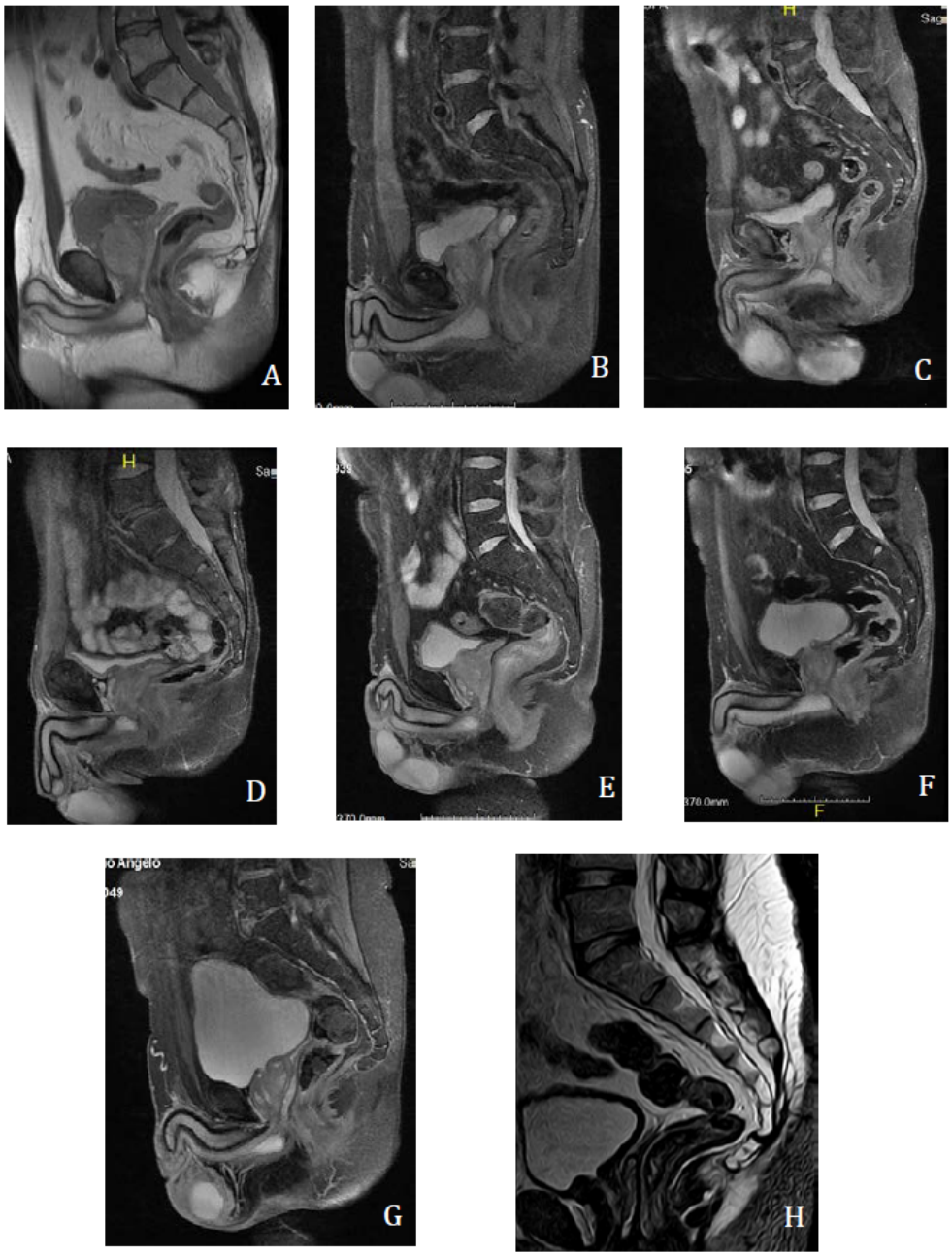



**Figure 18:** MRI of eight male patients diagnosed with PBNO enrolled in our research, sagittal view. A. 57-years-old patient; B. 54-years-old patient; C. 57-years-old patient; D. 42-years-old patient; E. 50-years-old patient; F. 45-years-old patient; G. 55-years-old patient; H. 42-years-old patient. The presence of a hooked coccyx was documented in all these patients.

## NEUROPHYSIOLOGICAL TESTING

Sacral reflex responses to electrical stimulation of penile nerves, pudendal nerve latency and concentric needle EMG were performed in n. 23/71 patients (32%). Tests were performed by experienced neurophysiologists. Three patients showed normal results, from both a neurologic and a muscular point of view, while 87% of the subjects (n. 20/23) presented a variable degree (from mild to moderate) of sacral and/or pudendal neuropathy, which could be either unilateral or bilateral.

EMG responses consisted in qualitative evaluations, thus no signal was recorded. Increased and/or unstable baseline activity, spasms with sustained contractions and/or poor post-contraction relaxations, and poor strength were demonstrated in subjects with hypertonicity of the pelvic floor.

In few patients we observed motor unit potential of irregular and polyphasic shape, in the absence of neuropathy signs. Other findings were altered proprioception, sympathetic hyperactivity and/or decreased endurance.

## PELVIC PAIN ASSESSMENT

Pain was found to be present in a relevant percentage of subjects enrolled in this research (76%). A deep clinical evaluation was carried out by dedicated physicians. Characteristics, entity and time of onset of pain were extremely variable among our study

population (12.64±10.87 months, mean±SD). Pain was reported to be distributed in different areas: lumbar muscles and vertebrae, sacroiliac joint, hip, coccyx, pubic bones, pelvic muscles, iliohypogastric, ilioinguinal, genitofemoral and pudendal nerves. A significant amount of patients presented a myofascial pain syndrome or articular pain, while neuropathic pain was found in only 5% of the studied patients. Ultrasound was always performed in order to exclude potential sources of pain due to nerve entrapments in fibrotic areas or neuromas.

A postural impairment characterized by increased lumbar lordosis, abnormal hip elevation, abnormal foot muscle mechanics without morphological abnormalities, sacrum rotation or altered postural control in response to external stimuli was found in more than 60% of the evaluated patients.

Following this initial clinical evaluation, anesthetic blocks were carried out to quantify and to qualify patient’s perception of pain modification. The anesthetic block test was considered positive if a >50% pain reduction was obtained. In case of persistent high clinical suspicion but no response to the anesthetic block (possible previous false negative block), the physician reevaluated the patient's symptoms and repeated the same procedure; otherwise, a different anatomic area was considered in case of lower clinical suspicion in the initial area. After the identification of the pain generator that is considered as the anatomical tissue that sustained the pain, the anesthetic block was repeated with the use of steroids to treat the inflammation and to prolong pain relief.

In our study population a significant pain relief was observed in all the subjects evaluated and treated.

## GAIT ANALYSIS EVALUATIONS

Mean patients' walking speed was 1.00 ± 0.07 m/s. Patients' gross pattern are synthetized in Table 4. As previously described in literature [Deluzio KJ, 1999], check marks (✓) and cross marks (✗) respectively represent accordance or discordance of the evaluated variable when compared to control. The synthetic score was obtained by summing all the check marks gained by the same patient.

We will not discuss in detail the results of all the seven patients analysed, as they were already published [Zago M/Camerota TC, 2017].

| Variable | Side | P1 | P2 | P3 | P4 | P5 | P6 | P7 | Variable score |
|---|---|---|---|---|---|---|---|---|---|
| *Ankle* | | | | | | | | | |
| Dorsi/plantar flexion | R | ✗ | ✗ | ✓ | ✓ | ✗ | ✓ | ✓ | 4 |
| | L | ✓ | ✗ | ✓ | ✗ | ✗ | ✓ | ✓ | 4 |
| In/eversion | R | ✗ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ | 4 |
| | L | ✓ | ✓ | ✓ | ✗ | ✗ | ✓ | ✓ | 5 |
| *Knee* | | | | | | | | | |
| Flexion | R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✗ | 6 |
| | L | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| *Hip* | | | | | | | | | |
| Flexion/extension | R | ✓ | ✗ | ✓ | ✓ | ✓ | ✓ | ✓ | 6 |
| | L | ✓ | ✓ | ✗ | ✓ | ✓ | ✗ | ✓ | 5 |
| Ad/abduction | R | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | 6 |
| | L | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | 5 |
| Internal/external rotation | R | ✓ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ | 5 |
| | L | ✓ | ✓ | ✓ | ✓ | ✗ | ✓ | ✓ | 6 |
| *Pelvis* | | | | | | | | | |
| Tilt | – | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | ✗ | 1 |
| Obliquity | – | ✗ | ✗ | ✓ | ✗ | ✗ | ✗ | ✗ | 1 |
| Rotation | – | ✓ | ✓ | ✓ | ✗ | ✗ | ✗ | ✗ | 3 |
| *Trunk* | | | | | | | | | |
| Flexion | – | ✗ | ✗ | ✓ | ✓ | ✓ | ✓ | ✓ | 5 |
| Bending | – | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | 7 |
| Rotation | – | ✗ | ✗ | ✓ | ✓ | ✓ | ✓ | ✗ | 4 |
| Gait score | | 12 | 10 | 16 | 12 | 10 | 13 | 11 | |

**Table 4:** accordance/discordance of individual gait variables in the seven patients studied, and related gait scores. R: right; L: left [Zago M/Camerota TC, 2017].

| Variable | Side | Participant | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | P1 | P2 | P3 | P4 | P5 | P6 | P7 |
| Walking speed (m/s) | - | 0.78 (0.02) | 0.80 (0.02) | 0.80 (0.03) | 0.66 (0.02) | 0.76 (0.02) | 0.69 (0.02) | 0.65 (0.04) |
| Step length (m) | R | 1.29 (0.03) | 1.32 (0.04) | 1.33 (0.04) | 1.09 (0.02) | 1.25 (0.03) | 1.14 (0.03) | 1.07 (0.07) |
| | L | 1.28 (0.03) | 1.34 (0.04) | 1.34 (0.05) | 1.11 (0.04) | 1.24 (0.07) | 1.15 (0.03) | 1.06 (0.06) |
| Step width (m) | - | 0.15 (0.03) | 0.17 (0.03) | 0.08 (0.01) | 0.13 (0.02) | 0.10 (0.02) | 0.09 (0.02) | 0.13 (0.03) |
| Duration (s) | R | 1.17 (0.02) | 1.27 (0.04) | 1.15 (0.01) | 1.22 (0.03) | 1.26 (0.06) | 1.16 (0.04) | 1.22 (0.05) |
| | L | 1.15 (0.03) | 1.27 (0.03) | 1.15 (0.02) | 1.22 (0.02) | 1.25 (0.07) | 1.17 (0.04) | 1.22 (0.05) |
| Stance phase (%) | R | 65.2 (0.8) | 61.2 (1.3) | 63.0 (1.2) | 66.0 (0.9) | 62.4 (0.9) | 62.3 (1.3) | 65.8 (2.0) |
| | L | 65.1 (1.0) | 62.8 (1.2) | 63.1 (1.3) | 65.7 (0.8) | 63.0 (1.3) | 62.6 (2.1) | 63.8 (1.9) |
| Swing phase (%) | R | 34.8 (0.8) | 38.8 (1.3) | 37.0 (1.2) | 34.0 (0.9) | 37.6 (0.9) | 37.7 (1.3) | 34.2 (2.0) |
| | L | 34.9 (1.0) | 37.2 (1.2) | 36.9 (1.3) | 34.3 (0.8) | 37.0 (1.3) | 37.4 (2.1) | 36.2 (1.9) |
| Double support (%) | . | 21.3 (1.3) | 14.3 (3.1) | 16.5 (1.1) | 23.2 (1.8) | 17.0 (1.9) | 16.4 (2.2) | 20.1 (1.7) |

**Table 5:** mean (SD) of extracted gait cycle parameters among the seven patients included in the study. R: right; L: left [Zago M/Camerota TC, 2017].

A general overview allows to identify the pelvis level (variable score: 1–3) as the variable more different from controls, followed by variables at the ankle level (variable score: 4-5). Interestingly, no patients presented deviation from normalcy when trunk bending or left knee flexion were evaluated, while only one patient presented an abnormal pattern at right knee flexion. On the other hand, hip variables presented a slight to minimal degree of discordance (variable score: 5-6). Looking at individual patients, P2 and P5 showed the greatest deviation from normality while P3 was the most concordant.

Table 5 reports individual parameters extrapolated from the GC: in term of spatiotemporal parameters, no macroscopic asymmetries nor discrepancies were detected among patients.

A description of the main issues of each patient has already been outlined in our previously published paper [Zago M/Camerota TC, 2017]. For synthesis, we will only briefly review the gait patterns of P1, P4 and P6, that appear to be the most significant. Moreover, the graphical representations of variables' behaviour in these subjects is of immediate visual comprehension.

- *P1*. The left ankle was extra inverted at heel strike and loading response (0–10% gait cycle), as well as in the pre-swing (50–60% GC). The right ankle was excessively inverted in mid and terminal swing phases (75–95% GC). The right hip was less flexed than in controls in the stance phase (0–60% GC), while the pelvis was backward tilted and clearly leaned on the left

side for all the GC. The trunk rotation patterns presented discrepancies in respect to normalcy [Figure 19].

- *P4*. The left hip was substantially more abducted than in controls for the whole GC. Pelvis obliquity exceeded normalcy bands from terminal stance to mid-swing, dropping on the left side. Pelvis also resulted overly clockwise rotated during all GC; concurrently, the trunk leaned backwards [Figure 20].
- *P6*. The left hip was excessively flexed in the stance phase, and both hips were overly abducted. The right hip was intra-rotated in the initial and mid-swing phase. The pelvis was clockwise rotated for all the GC [Figure 21].

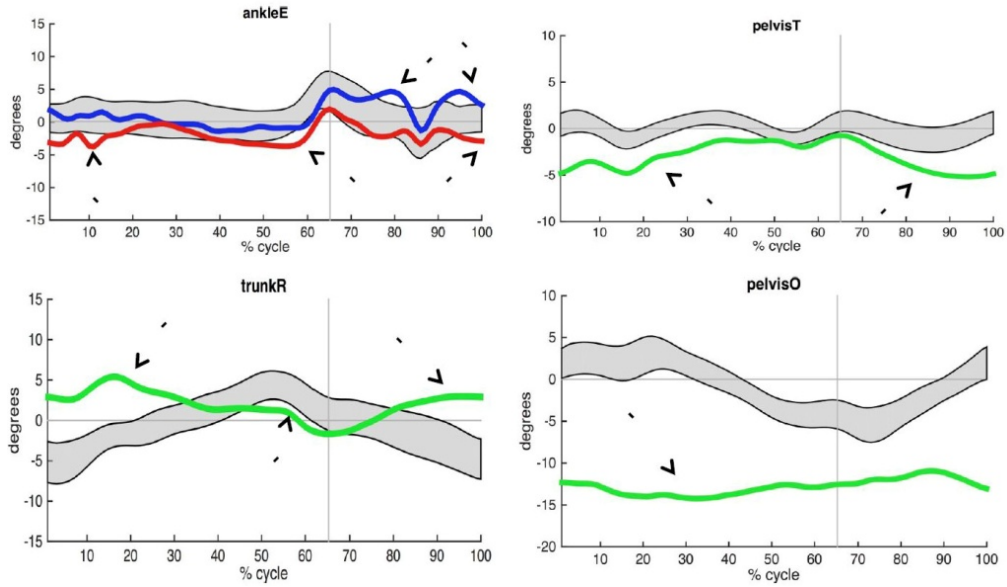



**Figure 19:** selected kinematic curves of P1. Grey bands: mean ± SD obtained from control subjects; ankleE: ankle inversion/eversion; pelvisO: pelvic obliquity; pelvisT: pelvic tilt; trunkR: trunk rotation [Zago M/Camerota TC, 2017].

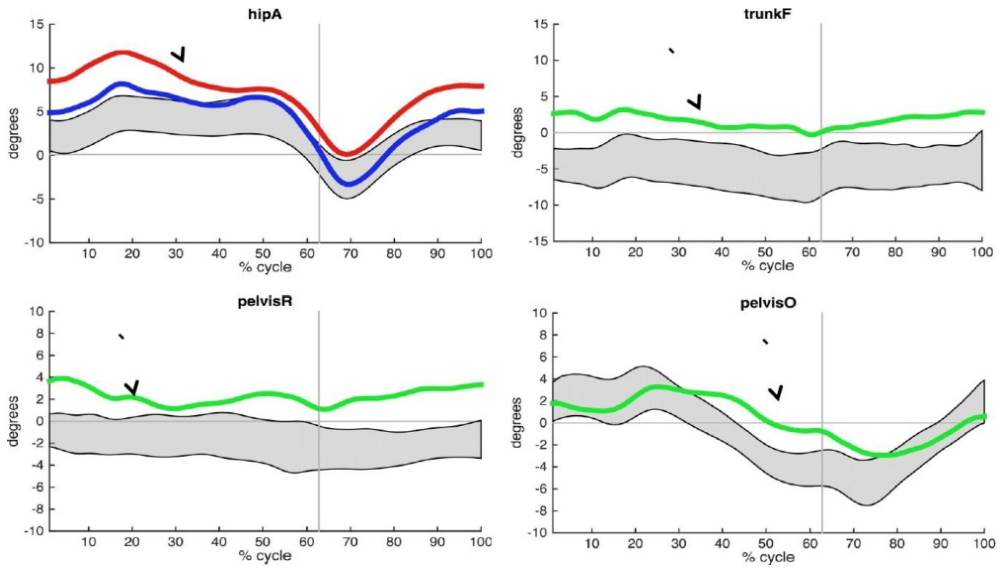



**Figure 20:** selected kinematic curves of P4. Grey bands: mean ± SD obtained from control subjects; hipA: hip abduction/adduction; pelvisO: pelvic obliquity; pelvisR: pelvic rotation; trunkF: trunk flexion/extension [Pisu S, 2015].

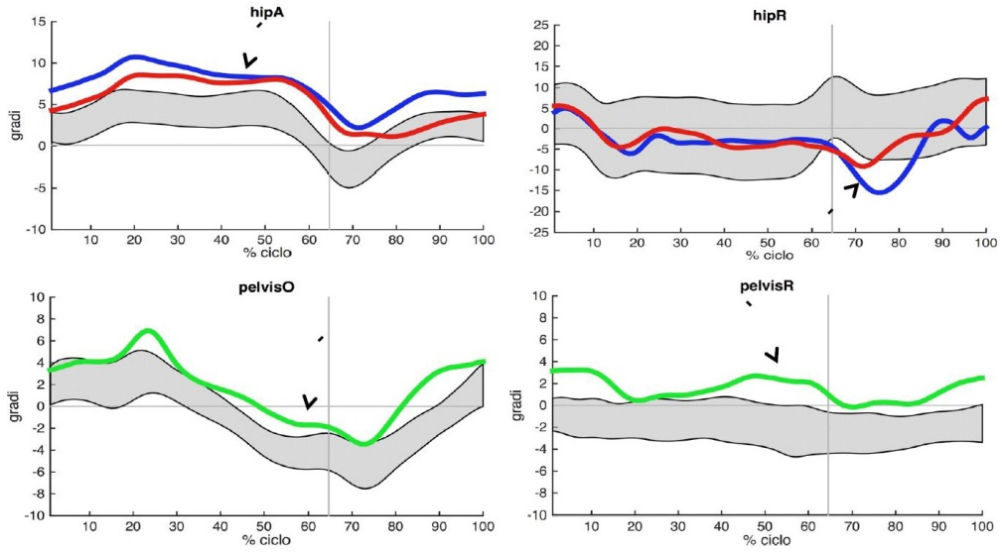



**Figure 21:** selected kinematic curves of P6. Grey bands: mean ± SD obtained from control subjects; hipA: hip abduction/adduction; hipR: hip rotation; pelvisO: pelvic obliquity; pelvisR: pelvic rotation [Zago M/Camerota TC, 2017].

## POST-TREATMENT RESULTS

Based on the clinical and diagnostic evidences presented, a comprehensive therapeutic approach was proposed and performed in our cohort of patients. Treatments consisted in:

- behavioural measures (such as education, avoidance of triggers, fluid intake regulation, stool management, etc), which represented the first approach to PBNO patients.
- intermittent catheterization, which is the insertion and immediate removal of a small urethral catheter few times a day to complete bladder emptying. This approach was only reserved to patients with high PVR, and was abandoned when low PVRs were obtained.
- rehabilitation strategies: rehabilitation or retraining of the hypertonic pelvic floor muscles (such as biofeedback techniques, reverse Kegel exercises, etc) and/or physical manipulations (physiotherapy, osteopathy) was of crucial importance in the treatment of PBNO patients.
- drugs: the pharmacological approach was variable and directed to obtain a myorelaxation (e.g. baclofen) or an improvement on allodynia (e.g. gabapentin, pregabalin). Tricyclic antidepressants (e.g. amitriptyline) have been proved to be beneficial for pain; therefore, they were administered to some PBNO patients with this intention, not to treat eventual depressive symptoms caused by chronic pelvic dysfunctions.
- trigger point injection therapy. When combined with continuous physical therapies this approach allowed to improve clinical results.

No traditional urological treatments (e.g. alpha-lytic drugs, bladder neck incision, etc) were proposed to any of the enrolled patients.

Post-treatment clinical outcome was collected in 25% of the study population (n. 18/71). Interestingly, when PBNO subjects were comprehensively treated (rehabilitation, myorelaxants, pain therapy, plantar in case of lower limbs dysmetria, etc.) an immediate improvement at bladder diaries was observed, as shown in Figure 22. Mean post-treatment volume emptied per single void was 285 mL (interquartile range 227.5 - 535.5).

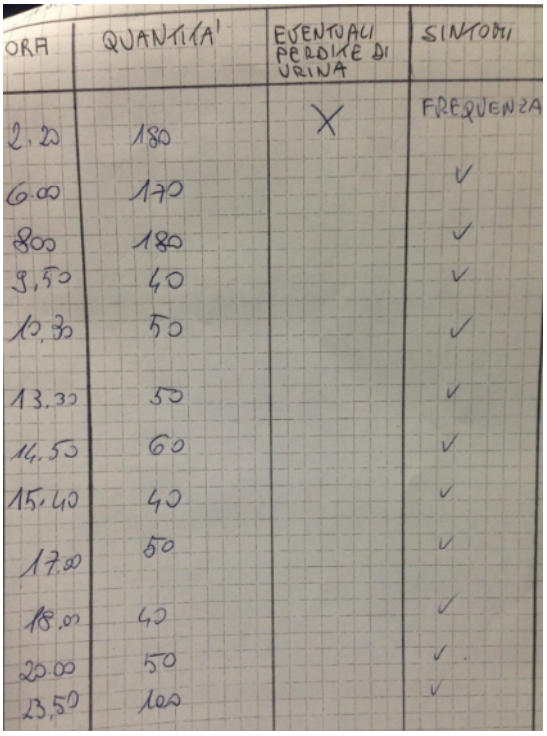



**Figure 22:** the presented voiding diary was filled by the same patient of Figure 9. It appears of interest to notice that after a rehabilitative period, there is a reduction in the number of micturition per day, and an increase in the volume emptied per single void. The greatest functional bladder volume is reached immediately after wake up.

Furthermore, post-treatment uroflowmetries showed the following characteristics:

- mean peak flow rate was 21.89 ± 9.20 mL/s (range, 7-40 mL/s);
- mean average flow rate was 9.67 ± 3.97 mL/s (range, 3–15 mL/s);
- mean post-void residual urine was 27.67 ± 62.45 mL (range, 0 – 250 mL).

Among these subject, 77% (n. 14/18) presented a normal uroflowmetric pattern, while 17% (n. 3/18) still had plateau flow, 11% (n. 2/18) urinary straining, and only one subject (5%) intermittent stream. The great majority of patients presented the association of more than one of these flow characteristics. Figure 23 shows pre- and post-treatment uroflowmetries of two subjects diagnosed with PBNO and comprehensively treated during our research. Case n. 1 was a 29-years-old male patient, duration of symptoms since 12 months, treated with exclusive physical rehabilitation. Case n. 2 was a 56-years-old male patient, duration of symptoms since 10 months, treated with physical rehabilitation, pain therapy and myorelaxant drugs.

A global significant improvement was noticed in all the post-treatment uroflowmetries collected. When a comparison among pre-treatment and post-treatment uroflowmetries was carried out in each single patient, statistically significant differences were noticed in PVR ($p=0.04$), in peak flow rate and in average flow rate ($p=0.0028$); voided volume showed a $p=0.14$. Summary statistics are presented in graphical form in Figure 24, Figure 25 and Figure 26 respectively.

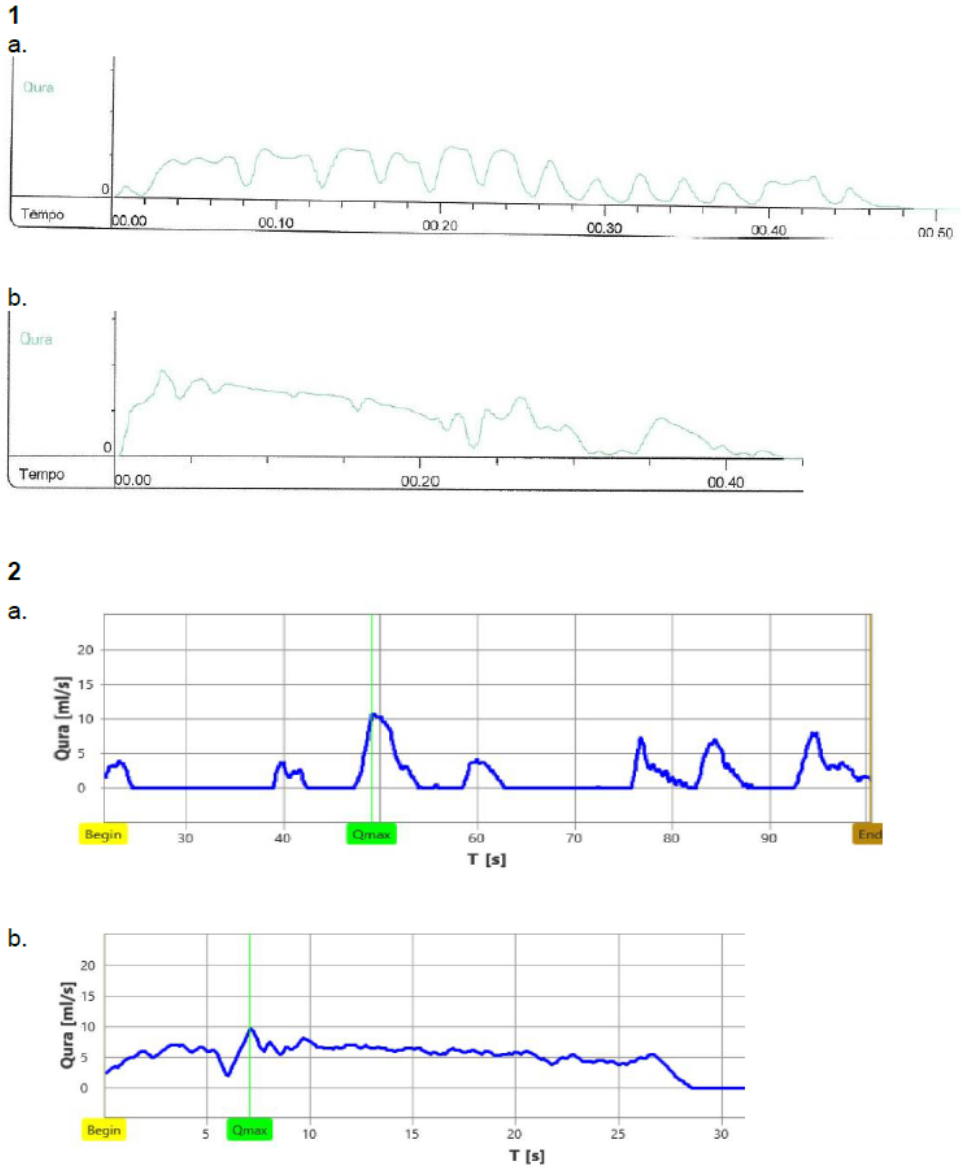



**Figure 23:** a visual comparison of pre-treatment and post-treatment uroflowmetries in two PBNO patients enrolled in our research. Each pair of images refers to the same patient: a. pre-treatment; b. post-treatment. 1. 29-years-old male patient, treated with exclusive physical rehabilitation. 2. 56-years-old male patient, treated with physical rehabilitation, pain therapy and myorelaxant drugs. Noteworthy in both cases is the regularization of the flow with the disappearance of intermittent stream.

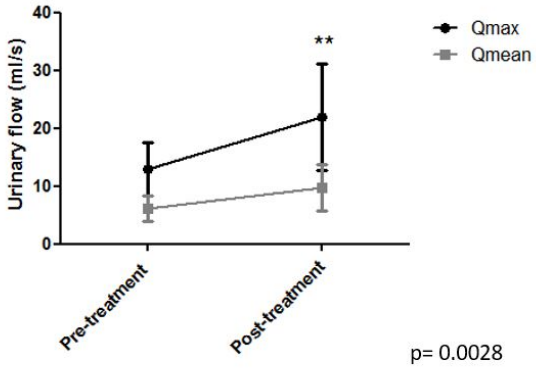



**Figure 24:** pre- and post-treatment modification of urinary flow parameters (peak flow rate and average flow rate, expressed in mL/sec) in 18 subjects enrolled in our research.

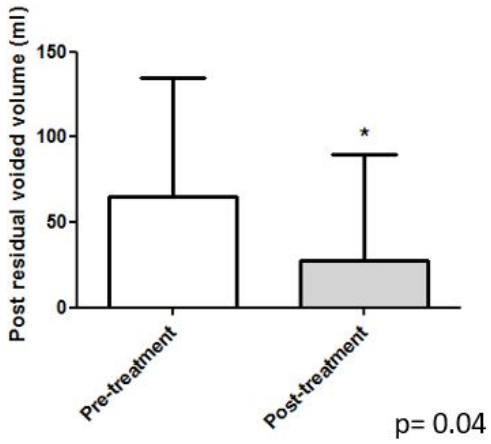



**Figure 25:** pre- and post-treatment modification of post-void residual urine (expressed in mL/sec) in 18 subjects enrolled in our research.

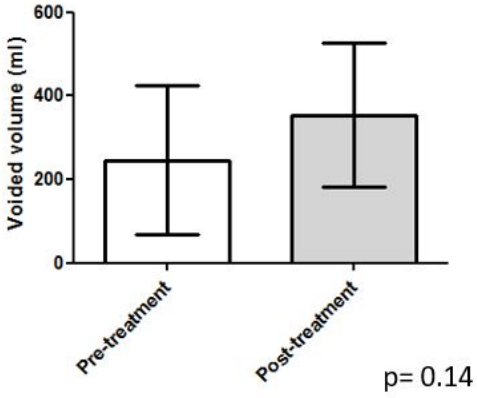



**Figure 26:** pre- and post-treatment modification of voided volume (expressed in mL/sec) in 18 subjects enrolled in our research.

# 3. DATA ANALYSIS AND INTERPRETATION

The more complex is the micturition disorder, the higher is the risk of wrong or incomplete diagnosis. Therefore, PBNO represents a challenging and scientifically underinvestigated niche of pathology. Moreover, numerous potential interference factors may occur in parallel with patient aging. Among these, we remember benign prostatic hyperplasia, diabetes, neurological diseases, cognitive impairment, interference due to drugs, constipation, alteration in metabolism and long-term effects of cigarette smoking. Therefore, PBNO might be an optimal study model in young patients, but certainly is a poor one in the elderly.

In addition to this limitation due to disease characteristics, it is important to remember that high-quality evidences are not always available when talking about urinary incontinence and voiding dysfunction in male patients. As nicely stated by Tubaro:

> "The problem with UI stem from it being both a symptom and a sign. Subjective (patient-reported) and objective (clinician-elicited) measures of UI can be used to both diagnose the condition and evaluate the outcome, with contradictory results sometimes reported when patient and surgeon opinions are compared" [Tubaro A, 2016].

In the period between November 2013 to October 2017 around 6.000 outpatient urological evaluations (first consultations and controls) in both sexes were performed by the same urologist (Tommaso Ciro Camerota). Among these, 71 male patients were

diagnosed to be affected by PBNO. Due to its size and strict selection, our study population represents a relevant case history.

PBNO is defined as a delayed and/or incomplete bladder neck opening. Under physiologic conditions, the urethral sphincter complex plays different roles, as it:

- provides adequate urethral resistance at filling phase to prevent urinary incontinence;
- exert an inhibitory action on detrusor, to postpone voiding;
- actively relaxes during micturition, in order to allow the voiding phase.

The above listed activities are also influenced by the contraction of other muscles or by the functioning of other pelvic organs. An unbalanced coordination among these numerous structures may lead to urethral sphincter dysfunction. A hypertonic or spastic urethral sphincter usually causes hesitancy and difficulty in initiating voiding, straining and/or incomplete voiding [Butrick CW, 2009b]. These characteristics may be nicely identified both at uroflowmetry (Figures 10, 11, 23) and morphologically confirmed at urethrocistoscopy (Figures 12 and 13). Reflecting a common pattern of innervation and a strict anatomical relationship, voiding dysfunction due to functional hypertonic urethral sphincter may also be associated with chronic constipation due to hypertonic anal sphincter. Moreover, a poor relaxation of pelvic floor muscles may result in a further inhibitory action on detrusor contraction (peripheral reflex). It was previously demonstrated that postural impairments or dysbehaviors may represent the triggers for pelvic floor hypertonicity, at least in females [Butrick CW, 2009b].

According to the available literature [Kaplan, 1994; Nitti, 2002; Camerota, 2016], the evidences provided with our research confirm that PBNO is characterized by a significant clinical heterogeneity. Voiding symptoms (e.g.: hesitancy, decreased force of stream, intermittent stream, incomplete emptying), storage symptoms (e.g.: frequency, urgency), or a combination of the both may be reported by patients at first presentation. Characteristics and severity of urological symptoms in our study population were already summarized in Table 3.

Frequency was the most common symptom in our study population (69%), coherently with previously published papers which showed a variable incidence from 74% to 79% [Yang SS, 2002; Grafstein NH, 2005; Glassberg KI, 2010]. Other common complaints were straining (65%), urgency (54%), feeling of incomplete voiding (58%) and intermittent stream (41%); nycturia and urinary incontinence were occasionally present.

None of the patient enrolled in our research presented previous or actual acute bacterial prostatitis; nobody had fever or urethral secretion at initial presentation.

The absence of urinary stimulus modifications (increased or decreased perception) in our study population allowed to intuitively exclude the presence of a neurological disease. In fact, the great majority of PBNO patients enrolled (97%; n. 69/71) reported a physiological perception of the urinary stimulus. This preliminary consideration was confirmed at subsequent investigations and specialist evaluations.

Pelvic floor integrity is fundamental for the maintenance of the heterogeneous pelvic functions both in males and in females. This integrity must be not only anatomic but also functional; in fact, even just a lack of coordination between contractions and relaxations may impact on storage/voiding of urine, storage/evacuation of faeces, sexual function (erection, ejaculation, arousal, etc) or pelvic organs support in females. Pelvic floor malfunction may be both negative (weakening) or positive (strengthening). In our clinical experience, hypertonic disorders are quite common – in both sexes – even if usually misunderstood. Gynaecologists are more used to evaluate pelvic floor integrity and functioning; unfortunately, this competence is not widespread as well among urologists, who basically underestimate the importance of pelvic floor muscles.

When specifically investigated, the majority of patients enrolled in our research reported worsening symptoms (mainly, frequency and urgency) during daytime, and a reduction of symptoms during night-time. This preliminary clinical feature represented an input for the Urologist to think about a functional disease. In fact, it appears of immediate comprehension that if an organic disease is present it should manifest during both the day and the night hours. To better understand this pattern, self-reported measurements were asked. The collected bladder diaries showed multiple low-volume voids during daytime, few to none voids during night-time, and normal voided volumes at first micturition after awakening (an example is presented in Figure 9). As previously shown in females [Weiss JM, 2001; Peters KM, 2006, Butrick CW, 2009c], hypertonicity of pelvic floor muscles may be confused and interpreted as a normal stimulus

to void. In this scenario, when subjects lie down – fact that usually occurs at night – intrapelvic pressure reduces, pelvic floor relaxes, and the false urinary stimulus disappears. Consequently, the bladder has the time and the physical space to fill up, and patients urinate when a proper voiding stimulus is generated at an adequate bladder volume. A prolonged upright position determines continuous solicitations to the pelvic floor, in association with the generated intra-abdominal and intra-pelvic pressures. In fact, due to the force of gravity, these pressures are discharged downwards inducing further increase in pelvic floor muscles activity. Moreover, several patients enrolled in our research reported an improvement not only on voiding symptoms but also on pain while they were in a supine position, suggesting a postural correlation for the both.

Before getting the proper diagnosis, many patients were prescribed with alpha-lithic drugs. Bladder neck is under control of adrenergic neurons; therefore, many clinicians believe that alpha-blockers may be a first therapeutic step. Unfortunately, very few patients perceived an improvement from such therapy, and it's quite common to see patient moving from a urologist to another to look for a more effective cure. All of the patients enrolled in this research were endoscopically found to have both internal and external urethral sphincter hypertonicity with a broad prostatic urethra. Based on this evidence, we do believe that alpha-lytic drugs are not working because they only act on the bladder neck, without any effect on the external urethral sphincter (rhabdosphincter). This is coherent with previously published data [Mishra VK, 1992].

Abdominal hernias (inguinal, umbilical, diastasis recti) are known to be the consequence of increased intra-abdominal or intra-pelvic pressures [Light HG, 1965]; moreover, hernia gate dimensions are directly linked to the severity of the generated pressures. Pelvic tilt, anteversion or torsion create continuous solicitations on the inguinal canal, and are recognised causes of its tearing. As previously shown, in our study population the incidence of abdominal hernias was relevant; 44% of the enrolled subjects (n. 32/71) presented actual or previously operated hernias. Although no side prevalence was identified, the laterality of inguinal hernias may depend on the characteristics of the scoliosis or pelvic torsion in each single subject. Therefore, in PBNO patients voiding symptoms and abdominal hernias appear to be as two sides of the same coin; both derive from a common pathogenic mechanism (postural impairment), thus we propose they should be considered as a unique syndromic presentation. Unfortunately, we do not know if BMI may represent a significant additional variable.

Many PBNO patients also reported heartburn in the absence of known diagnosed gastritis or gastroesophageal reflux disease. We decided not to investigate this finding during the research, therefore specific data were not collected. The most symptomatic patients were addressed to a gastroenterologist, for further clinical evaluation and eventual additional investigations. Even so, this symptom appears to be coherent with an increase of intra-abdominal pressures.

In our study population, more than one pain trigger was present in the same PBNO patient. We will not extensively discuss these aspects, considering that the topic of our research is voiding

dysfunction and not pain. Nevertheless, pain represents a relevant component of the initial clinical presentation in our cohort of patients (76%). After having excluded a visceral cause of pain, the urologist should refer the patient to specialised physicians, for a better qualification of the origin and the characteristics of pain. In our cohort of patients, myofascial pain syndrome or articular pain were predominant while neuropathic pain was found in only 5% of the studied subjects. Therefore, an accurate pain assessment is suggested in a second-level specialist pain centre. In fact, similarly to traumas, muscular hypertonicity represents an inflammatory trigger which induces local release of prostaglandins, histamine, serotonin and bradykinins [Butrick CW, 2009b]. This mediators act as sensitizers on muscle nociceptors; the result is the development of mechanical allodynia and hyperalgesia, also known as peripheral sensitization. It is also known that, in the presence of a prolonged noxious stimulus, neuroplastic changes occur in the central nervous system. These are characterized by the amplification of entity and/or area of the initial pain impulse, or by the generation of independent (spontaneous) pain impulses. This phenomenon is also known as central sensitization. Moreover, pelvic hypertonicity may result in myofascial pain syndrome [Butrick CW, 2009b].

When evaluating non-neurogenic LUTS, recommendations and guidelines are only available for men over 40 years-old [Gratzke C, 2015]. Therefore, younger patients usually require an individualized and more extensive approach. In our research, the diagnostic workflow adopted to study PBNO patients was not dissimilar to the one routinely used for patients affected by

neurogenic voiding dysfunction. We decided to avoid invasive investigations such as urodynamic evaluations, cystourethrography and extensive neurophysiological testing. According to the 5th International Consultation on Incontinence [Abrams P, 2013], no adjunctive relevant clinical or pathological information are provided by these procedures.

Not all the subjects reporting voiding dysfunction suggestive for PBNO underwent all of the described diagnostic procedures. In our experience, judicious selection of the diagnostic workflow is mandatory to avoid procedures which add little information. Clinical presentation, subjectively perceived bother, entity and relevance of reported symptoms (pain, bowel, others) by each patient represented the optimal driver to decide whether it was better to deepen diagnostics or to follow a more clinical approach.

In patients reporting LUTS, a deep investigation of general and urological history is mandatory as it should support the proper identification of the possible causes of reported disorder [Novara G, 2006; Irani J, 2003; McVary KT, 2011; Bosch J, 2013]. According to the current EAU Guidelines on Urinary Incontinence in Adults [Burkhard FE, 2016], the anamnestic report should always include details on type, timing, severity and reported symptoms of LUTS or UI. This accurate evaluation allows the physician to get a general comprehension on the reported voiding dysfunction and on its possible nature (e.g.: voiding/filling phase, obstructive/non-obstructive, incontinence/retention, etc.). Moreover, it helps in deciding whether the patient should be referred to other specialists to investigate additional symptoms as pain or bowel dysfunction. In the

end, the evaluation or exclusion of relevant comorbidities – as, for example, diabetes (both mellitus or insipidus), renal disease, urinary stones, neurological disease, drug assumption, etc – is essential to define the proper origin of the reported symptoms.

A careful characterization of the reported symptoms is strongly suggested. In fact, patients tend to focus only on a predominant symptom and have no complete perception of the complexity of the micturition discomfort or of other associated disorders (bowel or penile sensitivity alteration, pelvic or perineal pain or dysesthesia). Frequently patients realize their whole symptomatology during the urological evaluation; in this occasion, they also may discover correlations with daily activity or other dysfunction.

In our study population, an accurate physical examination was performed on all patients by the same urologist (Tommaso Ciro Camerota). The examination focused on abdominal, flank, pelvic and suprapubic evidences, in order to rule out conditions which may interfere with normal bladder voiding (e.g.: bladder overdistension/urinary retention, urethral meatal stenosis, urethral discharge, phimosis, etc.). Digital rectal examination was performed only in case of long-term presence of symptoms (more than two years), reported fever (to exclude prostatitis), age over 40 years-old, or in case benign prostatic enlargement was suspected. A deep neurological evaluation was performed by a pain management specialist (Matteo Leoni), in order to rule out neurological diseases. The incidence of abnormal anatomical findings was extremely low; in fact, cicatricial urethral stricture or benign prostatic obstruction were

excluded in all the patients. On the other hand, we frequently found what we like to call “non-classical abnormal anatomical findings” (e.g. hypertonicity), which were more consistent with musculoskeletal and postural aspects.

According to previously published data [McVary KT, 2006], the higher was patients’ impairment the more probable was the association with erectile dysfunction and/or ejaculatory disorders. The entity of the associated symptoms increases with LUTS severity [Rosen R, 2003], although the precise etiopathogenetic mechanism is not already known.

## VALIDATED QUESTIONNAIRES

In clinical research great attention is directed on the evaluation of patient-related-outcomes (e.g.: questionnaires). These may be of some help when the reported symptoms are vague, when the physician suspects an unreliable or uncompliant patient, or to monitor disease course during therapy. The most used questionnaires were International Prostate Symptom Score (IPSS) and International Consultation on Incontinence Questionnaire on Male LUTS (ICIQ-MLUTS).

Unfortunately, these tools only have a relative importance. In fact, they may be significantly influenced by patient’s psychological characteristics or patient’s expectations, being an important source for clinical biases. Many publications proved that evidences on questionnaire sensitivity is inconsistent [Chan SSC, 2013; Kim J,

2013; Tran MGB, 2013]. Moreover, it is well known that IPSS questionnaire has inadequate sensitivity and specificity to be used as a screening tool for urethral strictures when compared with urethroscopy. Previous publications have demonstrated an ability to identify only 38% and 23% of urethral strictures when IPSS cut-off was fixed respectively at >10 and >15 [Tam CA, 2016]. Moreover, in a group of men presenting with urethral strictures, it has been demonstrated that one on five patients (21%) doesn't' have symptoms identifiable by the AUA symptom index [Nuss GR, 2012]. This appears to be relevant for our study population considering that PBNO – being considered a functional (non-cicatricial) stricture – behaves like a urethral stricture.

For these reasons, we decided to administer validated questionnaires only with the intention to rule out the eventual coexistence of BPH or neurological diseases in our cohort of patients. Data obtained with questionnaires will not be shown in this publication as they are not objective reproducible measurements, and results must always be interpreted by the clinician. Moreover, consistently with cicatricial urethral stricture [Tam CA, 2016], some asymptomatic PBNO patients were observed in our study. Therefore, questionnaires are useless in the characterization of disease in these subjects.

## SELF REPORTED MEASUREMENTS

When initially evaluating a patient reporting LUTS or UI, it is advisable to look at urinary and bowel function as a unique entity. In fact, it's not infrequent to find that both the systems are affected in similar way (e.g. increase of frequency, retention, etc.). Moreover, symptoms and treatments of the urinary side may influence the intestinal side, and vice versa. In this scenario, bladder and bowel diaries appear to be helpful tools in guiding the clinician in the identifications of the pathogenic mechanism of disease.

In our experience, it was not possible to obtain frequency-volume charts from all the patients. According to previously published papers, patient's noncompliance was the major limitation to this diagnostic tool. In fact, it is not sufficient to collect a one-day diary to have an adequate overview on patient's habits; it is advisable to have at least a three-days registration bladder diary [Yap TL, 2007], and at least a ten consecutive days bowel diary.

The collected pre-treatment bladder diaries show the following characteristics:

- increased voiding frequency per 24 hours, mostly during daytime hours;
- preserved total volume per 24 hours, as expected;
- significant reduction of the volume per individual void (172.5 mL, interquartile range 141.3-287.8).

A comparison between pre- and post-treatment self-reported measurements shows a significant increase in the volume emptied per single void (post-treatment: 285 mL, interquartile range 227.5-535.5).

## UROLOGICAL INVESTIGATIONS

Being a simple non-invasive and office-based test, uroflowmetry was the first urological investigation asked in order to preliminary investigate the presence of LUTS and to identify characteristics useful to define a possible aetiology. Different diseases have variable degrees of deviation from normal morphology and flow parameters. When analysing a uroflowmetric report, urologist should always remember that micturition may be influenced also by external conditions such as bladder filling volume or emotion. Therefore, if a flow record is not coherent with the history of complains reported by the patient, it's always advisable to repeat the investigation at least twice. To reduce the impact of eventual psychological factors, all patients enrolled in this research made the exam in a private room, with no one else present.

Uroflowmetric measurements were performed accordingly with 2016 International Continence Society Good Urodynamic Practices and Terms [Rosier PFWM, 2017]. At the end of the exam, immediate post-void residual urine was measured. PVR measurement was always obtained by transabdominal ultrasound; we preferred this method to bladder scan or catheterization respectively because of its reliability/reproducibility and because of its non-invasiveness. All the diagnostic procedures were performed and interpreted by the same urologist (Tommaso Ciro Camerota).

Due to the lack of prospective scientific studies, to the great results variability among the same patient and to the influence that psychological factors may have, there is no consensus on the PVR threshold to define different therapeutic or diagnostic approaches.

According to previously published evidences [Siroky MB, 1980], we used PVR measurements as:

- a grade of compensation (no PVR) or imbalance (PVR >30mL) in PBNO patients;
- a follow-up tool to monitor residual urine under treatment (outcome), and to correlate symptoms with objective measurements.

In the present research, frequently observed pathological patterns at pre-treatment uroflowmetry were reduced voided volume and morphology of the curve characterized by the presence of a plateau flow and/or stream intermittency.

In our opinion, the presence of various morphological patterns at uroflowmetry reflects different clinical mechanisms leading to PBNO. Thus, we hypothesise the existence of two possible features of urethral sphincter complex hypercontraction: intermittent or continuous.

Although morphological patterns at uroflowmetry may not be considered pathognomonic, they are extremely coherent with the proposed aetiology of the disease. In rest conditions, both internal and external urinary sphincters are contracted. When micturition starts, under physiological conditions, detrusor muscle contracts while sphincters relax and open. If sphincters' widening is not adequate (but remains stable and constant) the urinary flow cannot reach its peak, conditioning a plateau curve. If instead urinary sphincters alternate contractions and relaxations, the curve will present interruptions (complete or partial). Trying to describe it from a simpler hydraulic point of view, let’s imagine a water cane we use in the garden to water flowers: if we determine a compression at the tip, the resulting output flow will be

constant (plateau); if instead we determine a cyclic and phasic compression at the tip, flow will present interruptions of different shape.

When evaluating voided volume, it is important to remember that uroflowmetric parameters are traditionally considered reliable when more than 150 mL of urine is voided [Kranse R, 2003; Jorgensen JB, 1992]. In PBNO patients it may be extremely difficult, or in some cases impossible. Due to the increased urinary frequency and/or to the increased perception of bladder fullness, these patients usually present a reduction of voided volume per each bladder emptying. But when considering the sum of voided volume and post-void residual urine, the full bladder filling volume before uroflowmetry usually appears to be more than adequate (being quite always more than 150 mL). Therefore, the collected uroflowmetries are considered reliable. Morphology and shape of the uroflowmetric curve may be influenced by emptied volume, but if the total volume (voided + PVR) is adequate the test is reliable.

Some of the more representative uroflowmetric patterns observed in our study population were reproduced in Figure 10 (intermittency) and in Figure 11 (plateau flow).

When analysing PBNO patients before and after treatment, our outcome measures were:

- improvement in uroflowmetric parameters (peak flow rate, average flow rate, PVR, and morphology of the curve);
- reduction or disappearance of pain, when present at first consultation;
- improvement in bladder diaries or in patient's perceived discomfort.

An increase in voided volume and a normalization of the curve shape was observed in all the uroflowmetries collected after rehabilitative treatments (25%, n. 18/71). Two examples are shown in Figure 23. In our opinion, these results were not influenced by the higher volume voided. In fact, as already reported before, pre-treatment bladder filling volumes were adequate; the same was noticed in the post-treatment uroflowmetry, but with a significant reduction (up to disappearance) of PVR. This evidence supports our hypothesis that modifications in pelvic static determine an increase in intrapelvic pressures with a consequent reduction of physical space for the bladder. The final effect is a reduced functional bladder capacity. This mechanical and physical aspect is evident at MRI imaging, as shown in Figure 27. Moreover, if the rectal ampulla is overextended – as it frequently happens in PBNO patients, due to the coexistence of bowel voiding dysfunction or constipation – bladder may even have less space.

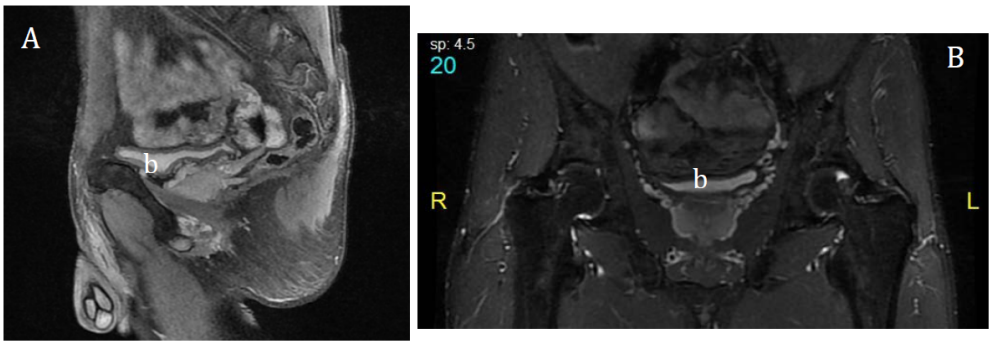



**Figure 27:** MRI of a 42-years-old male patient diagnosed with PBNO. A. sagittal view of the pelvis. B. frontal view. Bladder (b) is compressed downwards by the pelvic conformation.

Invasive procedures are justified if uroflowmetry shows pathological results in patients with bothersome symptomatology [Nitti VW, 2002]. In PBNO patients urethrocystoscopy allows to exclude cicatricial urethral strictures, benign prostatic obstruction, transitional cell carcinoma of the bladder or vesical stones. Endoscopically, not only the internal urinary sphincter (bladder neck) but also the external urethral sphincter (rabdosphincter) was found to be contracted. All the patients enrolled in this doctoral research endoscopically presented small non-obstructive prostate, and the absence of urethral strictures. We frequently observed the presence of bladder wall trabeculation resulting from high pressures generated by the detrusor to overcome sphincters' resistance; in few cases initial bladder diverticula were also observed.

Previously published papers described a low probability of positive findings on cystoscopy in men younger than 50 years-old reporting LUTS [Toh KL, 2006]. Our results are in contrast, demonstrating a high incidence of endoscopic functional alterations (external and internal urethral sphincter hypertonicity), as shown in Figures 12 and 13. This non-concordance may depend from patients' selection criteria, and might be amplified by the experience we have gained over the past years in clinically evaluating young male patients reporting LUTS. In fact, we only decided to perform urethro-cystoscopy when PBNO was suspected at uroflowmetry, bladder diaries and patients' reported symptoms, reducing the number of potentially non-useful procedures.

Urodynamic evaluations were not performed in our cohort of patients. In clinical trials, it has been demonstrated that this procedure

has low sensitivity, specificity or predictive value as first level test [Rosier PFWM, 2013b]. Moreover, according to the recommendations of the 5th International Consultation on Incontinence [Rosier PFWM, 2013a] urodynamic is only advised:

- when its results may change clinical management;
- after treatment failure (if more information is needed to plan a therapy);
- as long-term follow-up of neurogenic lower urinary tract dysfunction or in complicated incontinence [Lucas MG, 2012].

None of these conditions were present in our study population; therefore, we decided not to carry out the procedure.

Cystourethrography is a radiologic exam useful in the diagnostic of cicatricial urethral strictures, which represented one of the exclusion criteria for the enrolment of patients in this research. In the diagnostic workflow of PBNO patients, we always performed an outpatient flexible urethroscopy which resulted appropriate and adequate to make a diagnosis. Therefore, cystourethrography was never asked in our study population.

## NEUROPHYSIOLOGICAL TESTING

Observations obtained with our research showed the presence of a variable degree (from mild to moderate) of sacral and/or pudendal neuropathy, which could be either unilateral or bilateral. None of the 23 patients studied with neurophysiological procedures had a clear nerve injury, but only a malfunctioning along

pelvic nerves path. These evidences are consistent with previously published observations in women with pelvic floor disorders [Walters MD, 2014]. Three subjects showed normal results.

Increased and/or unstable baseline activity, spasms with sustained contractions and/or poor post-contraction relaxations, and poor strength were demonstrated at EMG in our study population. These evidences are consistent with previously published researches in females diagnosed with hypertonic pelvic floor and perineal pain (vestibulitis) [White G, 1997]. Moreover, a prolonged pelvic floor electromyographic interval between pelvic floor relaxation and urine flow start was found in our cohort of patients. From a clinical point of view, this mechanism is perceived as a prolonged initial hesitancy, as already described in literature [Grafstein NH, 2005].

Motor unit potential of irregular and polyphasic shape were observed, in the absence of signs of neuropathy. This is an indirect sign of rearrangements of motor unit fibres, which is typical of slowly progressing processes [Zalewska E, 1998]. Other findings were altered proprioception, sympathetic hyperactivity and/or decreased endurance. No recurrent pattern was identified. A possible explanation for this variability is that the mechanisms of adaptation may vary from a subject to another. An alternative possible explanation involves spinal cord hyperexcitability, which was already proposed for the explanation of some kind of pain. Unfortunately, no reliable scientific evidences are already available; in fact, this is a complex field and hypotheses can be verified with extreme difficulty.

Neurophysiological testing (concentric needle EMG, sacral reflex responses to electrical stimulation of penile nerves, pudendal

nerve latency) were initially asked in our diagnostic work-up. As far as the comprehension of PBNO and its possible etiopathogenesis were increasing, we decided to avoid patients from performing these annoying invasive procedures. In fact, nor they provided adjunctive significant clinical information, neither their results modified the following clinical approach. Finally, in our study population only 5% patients presented neuropathic pain, while 95% presented a myofascial pain syndrome or articular pain.

## IMAGING

*Abdominal ultrasound*

Although it is not considered mandatory in the evaluation of PBNO patients [Ackerman AL, 2012; Gratzke C, 2015], upper urinary tract evaluation with abdominal ultrasound was always performed. In fact, this first level imaging gives no radiation to patients and provides useful clinical information. None of the patients enrolled in this research presented hydroureteronephrosis, upper urinary tract stones or transitional cell carcinoma of the bladder.

*X-rays*

X-ray scans were performed in different Centres, according to patient's preference; images were re-evaluated by the same urologist (Tommaso Ciro Camerota). Traditional full spine X-ray imaging provided interesting data in our study population. All the PBNO patients studied (n. 35/71, 49%) with this procedure showed discordance from normalcy. Obturator foramina asymmetry reflects

pelvic torsion, which was subsequently confirmed at gait analysis. Cervical spine rectification, increased sacral slope, reduction of thoracic kyphosis and other changes in spino-pelvic parameters are known compensatory mechanisms to lumbar lordosis modifications [During J, 1985; Jackson RP, 2000; Roussouly P, 2005; Vaz G, 2002]. In few patients we also found a partial or complete congenital sacralization/hemisacralization of L5, which is defined as the fusion of the first sacral vertebra and the 5th lumbar vertebra.

These possible modifications were not present all together in the same patient. In fact, in our study population we observed a significant variability which, according to the available literature, must be attributed to patient's age, to the musculature status, to painful phenomena and/or to the severity of the underlying imbalance [Barrey C, 2013]. Compensatory mechanisms of the spine are usually associated with aging. However, spine adaptations should be differently analysed in PBNO patients. These subjects are in fact relatively young (30 to 50-years-old); therefore, compensatory lumbar discopathy or increased sacral slope must be interpreted as the consequence of a biomechanical imbalance, not depending on degenerative aspects.

*MRI*

Magnetic resonance imaging is a widespread imaging technique which provides detailed information on morphological aspects of the pelvic structure (bones) and its content (rectum, bladder, prostate) other than the pelvic floor [Woodfield CA, 2010]. It offers clear anatomical details in three possible views (axial, coronal and sagittal) [Hoyte L, 2004; Pescatori M, 2008], for some aspects

even better than the more classical anatomical dissection studies. Unfortunately, there is no standardised interpretation of results among radiologists [Lockhart ME, 2008], limiting the technique potentiality in the daily clinical practice. In our experience, the precious collaboration with an expert Colleague – Dante Broglia, who is both radiologist and orthopaedic – provided and granted incredible resolving information for setting up an accurate and precise diagnosis.

The identification of pathological characteristics on MRI was based on known morphological presentation in the normal male and on comparison with anatomy. Twenty-one patients in our study population were submitted to MRI of pelvis and perineum with either 1.5 or 3 Tesla scanners. 3 Tesla magnetic resonance is more powerful but – when compared with 1.5 Tesla – it required more time for image acquisition. Moreover, being more powerful, 3 Tesla skeletal and muscular images may be afflicted by an increased rate of false negative and false positive results. Therefore, 1.5 Tesla scanner appear to be superior for muscular and skeletal studies, while 3 Tesla scanner is optimal for the functional imaging of the brain and spinal cord (but not for the peripheral nervous system).

All the subjects presented various degree of discordances from normalcy. Some of these pathological aspects were recurrent, but unfortunately a unique common pattern was not identified. Nevertheless, we were able to categorize abnormalities into four groups:

1. hypertrophy or hypertonicity of pelvic floor muscles, which were present – with different degrees – in all the 22 subjects;

2. tendon inflammation;
3. joints (e.g. sacroiliac or pubic symphysis) inflammation or sclerosis;
4. skeletal abnormalities as for example anterolisthesis, hooked coccyx, posterolateral disc protrusion at lumbar spine or femoroacetabolar impingement.

We believe that a possible explanation to this heterogeneity is that many different conditions may affect the normal postural setting. The consequent pelvic instability lead to pelvic floor muscles hypertonicity, which is in the end responsible for PBNO. Recurvatum coccyx was found to be present in 15 of the 22 subjects who underwent MRI (68%), which is consistent with our results obtained from full spine X-ray performed in another group of 35 patients with PBNO. This morphologic modification suggests the presence of a chronic condition, which had time to shape the coccyx. The underlying proposed mechanism will be explained afterwards in this section.

Another frequent observation was the evidence of an anococcygeal raphe thickening. This condition was usually associated with a reduction in the rectal angle due to anococcygeus muscles hypertonicity. Consequently, the rectum was lifted up, as shown in Figure 16.

In few subjects, greater sciatic foramen's dimension was found to be reduced due to piriformis muscle increased tone. At this level the sacral plexus gives off the pudendal nerves. Therefore, in these patients PBNO may not only derive from a pelvic floor muscle

hypertonicity, but it may also be sustained by a secondary pudendal nerve malfunctioning.

In one patient we found MRI evidences of a compression on membranous urethra carried out by a hypertonicity of deep transverse perineal muscle. This compression was present immediately below the external urethral sphincter, as shown in Figure 17.

The relationship between urinary sphincter shape and function was previously investigated in females [Morgan DM, 2009]; women with larger striated muscle measures (dimension, length, area) were shown to have greater urethral elevation. This datum reflects levator ani muscle function more than its anatomy, Interestingly, with increasing age it was noted a shortening in the striated muscle sphincter length. In male, sphincter's volume was only evaluated with the intention to predict outcome after surgery [Digesu GA, 2009; Nguyen L, 2008].

None of the publications on the use of MRI in patients affected by LUTS or UI proved a benefit from the adoption of this diagnostic procedure. All the investigations were focused on finding a correlation with clinical outcome after treatment. In our opinion MRI might play an important role in properly diagnose a disease more than in defining the final outcome. Why a pubococcygeus muscle should be hypertrophic? Does a sacroiliac joint dysfunction correlate with a voiding dysfunction or with pelvic-perineal pain? Understanding the cause/effect sequence may contribute to the identification of a better therapeutic workflow which necessarily requires multidisciplinary competences to be managed. The evidences provided with our research represent an input to change approach and perspective on a

known topic; a new point of viewmay in fact represent an inevitable step for a better comprehension.

The actual lack of evidences on the potential usefulness of MRI images in evaluating LUTS or UI principally depends on the absence of standardisation on measures and radiological reports. But it doesn't seem unrealistic that a more in-depth knowledge of the technique applied to urological aspects could allow its widespread use, similarly to what happened in other disciplines. In coloproctology, more than ten years ago anatomical and functional patterns were identified at MRI imaging, with the consequent development of standardized evaluations. When assessing rectocele or obstructed defecation, dynamic MRI imaging technique is able to show modifications in anorectal angle during squeeze and during defecation [Fletcher JG, 2003; Bharucha AE, 2005; Bharucha AE, 2007]. Contractions and relaxations of the puborectalis muscle are responsible for these changes, while contractions of pubococcygeus, ileococcygeus and ischiococcygeus muscles are responsible for cranio-caudal movements of the anorectal angle. This radiological investigation – known as dynamic MR defecography – plays a central role in the diagnosis of pelvic floor dysfunction, and has a direct clinical impact when assessing therapeutic decisional aspects (conservative versus surgical).

Full spine X-ray and pelvic/perineal MRI proved similar skeletal findings in our study population (e.g.: horizontalization of the sacrum, hooked coccyx, sacralization of L5 vertebra, etc.). Moreover, MRI was able to add information on soft tissues (muscles and tendons) and inflammatory patterns at joints (e.g.: sacroiliac).

Therefore, we believe that not all the male patients with a suspicious of PBNO must undergo both the diagnostic procedures. Imaging should be selected on the basis of quality and severity of reported symptoms at first presentation (e.g.: pain), or should be reserved for subjects in which initial treatments were ineffective or for patients whose symptoms got worse in time.

## GAIT ANALYSIS EVALUATIONS

When looking at the results of the performed evaluations, one of the main findings of our research is that patients with voiding dysfunction may present a variable degree of abnormal kinematic gait patterns. In particular, we recorded gait cycles of seven self-selected subjects already diagnosed with PBNO, and we were able to quantitatively detect deviations at the ankle and pelvis level with respect to normal subjects. Four patients differed from controls in more than a third of the variables, two patients presented a mild discordance, while only one patient (P3) was almost comparable to normal subjects.

Interestingly, P3 not only was the patient with the highest gait score (i.e. smaller deviation from normalcy), but he also was the one with the lowest subjectively perceived urological impairment; in fact, when investigated, he only reported urinary frequency and terminal dribble, with no other associated voiding symptoms. Unfortunately, we were not able to find a direct correlation between the severity of the urological symptomatology reported and the obtained gait score per

each patient. This probably depends on sample size and on intrinsic PBNO clinical heterogeneity.

Postural defects were not subjectively perceived by any of the seven participants in the gait study. In fact, all patients were completely asymptomatic from a musculoskeletal point of view. A possible explanation for this clinical evidence is that – as it happens for urological symptoms, which are usually underestimated or not recognized if present since a long time – chronic modifications of a physiological behaviour may be scarcely perceived. A day by day adaptation to a slowly arising condition makes it more difficult for a patient to be fully aware of the eventual degree of deviation from normalcy. Moreover, as it was recently proposed, the self-perception of a chronic disease may also be influenced by the degree of dependence that the subject has from services or other persons (family, nurses, doctors, etc.) [Adrián-Arrieta L, 2017]. According to this evidence, none of the seven patients evaluated with gait analysis – as well as none of the 71 subjects with PBNO enrolled in this research study – perceived a functional limitation of movement; moreover, nobody has previously required specific postural or orthopaedic evaluations.

## FOLLOW-UP AFTER TREATMENTS

Basing on the produced evidences, a comprehensive approach was used to treat PBNO patients enrolled in this research. Rehabilitation strategies were more effective when behavioural measures and drugs or trigger point injection therapy were adopted. Furthermore, no traditional urological treatments (e.g. alpha-lytic

drugs, bladder neck incision, etc) were proposed to any of the enrolled patient.

These treatments provided good results. All the subjects evaluated after treatment showed an improvement in reported symptoms, bladder diaries and in all the uroflowmetric variables (voided volume, peak flow, average flow, PVR, morphology of urinary flow). Urethrocystoscopy was not repeated due to its invasiveness; moreover, we believe that it would not have added any further useful information.

Unfortunately, we were able to analyse pre- and post-treatment clinical and uroflowmetric characteristics only in 25% of the patients. This was due to different reasons:

1. as far as the research was progressing, we acquired more knowledge on the disease and on its clinical features. Therefore, subjects initially enrolled in the study received different treatments or were evaluated by different physicians (while the Urologist remained always the same);
2. few patients asked to perform physical treatments in other Centres, thus we were not able to verify the quality of the provided rehabilitative procedures;
3. the great majority of patients is still under treatment, therefore we expect to get more post-treatment uroflowmetries and bladder diaries in the upcoming months. In fact, based on the evidence that PBNO is a chronic disease, we decided to perform a urological revaluation assessment not earlier than 4-6 months after rehabilitative treatments started.

In addition, we also have a small group of non-responders on a clinical basis (perceived symptoms). We do not know if this depend on psychological aspects, on a too short period of treatment, or on neurological peripheral reflexes deriving from locally generated allodynic triggers. Intuitively, we think that the more prolonged was the clinical history of PBNO patients, the longer and complex should be the comprehensive therapeutic approach. Therefore, in these patients rehabilitative treatments will be continued for few more months, in order to observe if an improvement is possible. In case of persistent pelvic dysfunctions, sacral neuromodulation may represent a possible option for these subjects, with the intent to down-regulate neuropathic changes highlighted at neurophysiological tests. Although it was previously proposed as an experimental procedure for PBNO [Goldman HB, 2006], to date no definitive data are available. Moreover, when considering this approach as a possible treatment for pain, a paper reported an improvement in up to 50% of patients with chronic pelvic pain [Mayer RD, 2008], while another study demonstrated a general improvement in quality of life in 85% of patient with interstitial cystitis [Peters KM, 2002].

# III. NEWLY PROPOSED ETIOPAHOGENIC MECHANISM FOR PBNO

The relationship between urinary continence and posture was previously proposed and evaluated in a female population. Seventy patients who underwent trans-obturator tape for urinary incontinence were studied, and better functional results (obtained post-operative urinary continence) were noticed when a lower angle of pelvic inlet orientation was present [Sahinkanat T, 2011]. These preliminary clinical results are coherent with earlier publications in which anatomic details of the pelvis (pelvic openings' diameters) were proposed as determinants of pelvic organ prolapse [Nguyen JK, 2000] and urinary incontinence in women [Stav K, 2007]. Increased pelvic diameters among women affected by urinary incontinence may be both congenital or acquired with age. In the latter case, it has been suggested that this anatomical modification would depend from a change in the sacral inclination. Unfortunately, to date no definitive explanation has already been found [Amonoo-Kuofi HS, 1992].

In addition, affections in the musculoskeletal system were previously proposed as influencing elements in other pelvic dysfunctions such as chronic pelvic pain in male patients [Segura JW, 1979; Salvati EP, 1987; Hetrick DC, 2003] or anal incontinence in both male and female patients [Altomare DF, 2001]. In females, variations in the contractility of pelvic floor muscles and in the generation of intra-pelvic pressure may occur in case of

maladjustment of the lumbo-pelvic area [O'Sullivan PB, 2002; Hungerford B, 2004; Bø K, 2005].

An improvement in urinary continence was retrospectively observed in 11/12 patients who underwent a surgical procedure (spinal fusion or total hip replacement) for severe low back pain. Unfortunately, no anatomical or functional evaluations were performed to better understand the nature and the characteristics of the urge urinary incontinence clinically reported by patients, although neurologic or genitourinary diseases were already excluded [Eisenstein S, 1994]. Finally, another epidemiological study proposed the association between low back pain and lower urinary tract symptoms in males, but no statistical significance was proved [Koskimaki J, 2001].

The above-mentioned publications focused on urinary incontinence, pain and pelvic organ prolapse. To the best of our knowledge, no previous scientific study proved a correlation between postural defects/modifications and bladder voiding disorders in the male population (e.g.: urgency, frequency, intermittency, etc.). The Finnish study [Koskimaki J, 2001] was the only one to have included males, but it differs from our research for the variables under evaluation: Authors were searching for an association between back pain and voiding dysfunction, while we are hypothesizing a correlation among postural impairments and voiding dysfunction. In fact, on one hand we know that back pain may derive from different causes, not necessarily correlated with a postural defect; on the other hand, a postural impairment may be completely underestimated or not

recognized by the subject under evaluation, mainly due to the absence of clinical symptoms.

Based on these considerations, we previously hypothesised the existence of a possible correlation between altered biomechanics of the pelvis and urethral sphincters activity in male patients reporting voiding dysfunction in the absence of neurological or orthopaedic signs [Camerota TC, 2016]. The results of this doctoral research show that gait variables at ankle and pelvis level were vastly discordant from normalcy, while gait variables at knee and trunk level were little-to-no interested. In our cohort of patients, the 5 subjects (P1, P2, P4, P5, P7) who presented ankle discordances also presented pelvic discordances at any of the three possible gait variables. Only P3 and P6 presented pelvic discordance with no ankle involvement. A possible explanation for this evidence is that a foot support disorder (e.g.: flatfeet) or a dysmetria of the lower extremities may determine an alteration to the static and to the dynamic of the pelvis, without causing any alteration at the knee level.

In our hypothesis, a modification in the normal static posture of the pelvis (for example, in the case of anteversion, retroversion or torsion, as shown in Figure 28) invariably determines a variation in the contractile state of the pelvic floor muscles. This support system behaves like a hammock between two trees: a movement in the structural part induces an adjustment on the elastic side. In the case of PBNO, we propose that the urethral sphincters hypertonicity might depend from a hypercontraction of the entire pelvic floor, due to an adaptation sustained by a modified static of the pelvis.

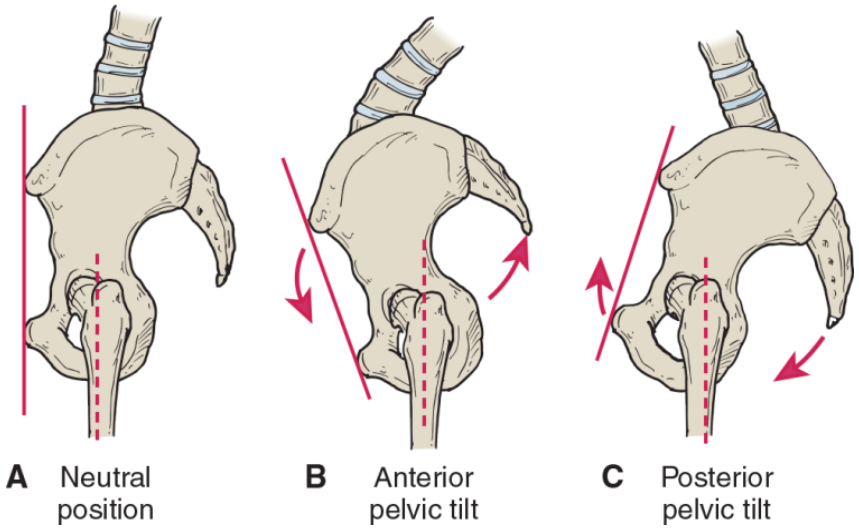



**Figure 28:** schematic representation of possible modifications in the static of the pelvis, lateral view. A: physiologic condition. B: anteversion. C: retroversion [Kisner C, 1996].

Moreover, when magnetic resonance imaging was performed in a group of consecutive subjects enrolled in our research, it was frequently observed a hypertonicity of muscular structures of the perineal plane and/or a variation in the angle of inclination of the coccyx. The hypertonicity was often asymmetric, with no prevalence of a side over the other. Looking back to the anatomy presented in the introductive chapters of this publication, pelvic floor muscles posteriorly attach to the apex of the coccyx. Coccyx is fixed to the sacrum by a fibrocartilage disc to create the sacrococcygeal joint. This structure – which is also known as the interosseous ligament – allows a certain mobility to the joint (15° of flexion, 13° of extension), although it certainly appears limited when compared to that of other skeletal segments. The normal behaviour of the sacrococcygeal joint under physiological conditions was previously described [Weiselfish Giammatteo S, 2003], and is reproduced in Figure 29:

- when the sacrum extends, the apex of the coccyx flexes and moves anteriorly;
- when the sacrum flexes, the apex of the coccyx extends and moves posteriorly.

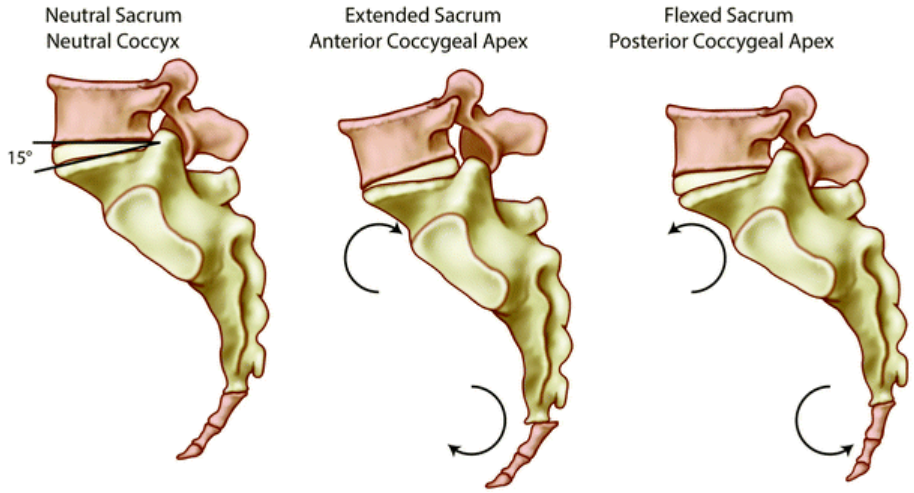



**Figure 29:** proposed physiological biomechanics of the sacrum and the coccyx [Weiselfish Giammatteo S, 2003].

An increased activity of the pelvic floor muscles may determine a modification of the coccygeal curvature; in our patients, this modification was evident both at MRI and at traditional X-ray imaging, as already shown in Figure 18.

Moreover, when we evaluated the full spine X-ray in two projections of the seven participants to gait analysis, we observed various discordant aspects from normality (e.g.: slight pelvic upslip, moderate sacral horizontalization, or scoliosis). These characteristics are coherent with previously published evidences. In fact, it is known that poor posture contributes to pelvic floor muscle shortening or tensing. For example, in the case of stooped posture, the coccyx is further flexed causing a passive shortening of the pelvic floor

muscles. This modification determines a change in the resting length of the pelvic floor muscles, leading to a hypertonic pelvic floor [Padoa A, 2016]. Another example is represented by hyperlordotic posture. In this scenario, intra-abdominal pressure rises resulting in an increased solicitation for the perineal plane; thus, pelvic floor muscles become overactive in order to counteract these forces.

The pathogenic mechanism we are proposing to be involved in PBNO patients is mirrored to the one already described for stooped posture. In fact, we suggest that pelvic floor muscle shortening does not depend on the flection of the coccyx. We rather believe that the mechanism is the opposite: muscular hypertonicity is responsible for a modification of coccygeal appearance.

Another frequent finding at MRI was a sacroiliac joint dysfunction or inflammation. These data are consistent with previous publications which suggested a role of pelvic floor muscles on spinal stiffness [Hodges PW, 1997; Shirley D, 2003; Essendrop M, 2004; Cholewicky J, 1999a,b]. An increased muscular activity may work on sacroiliac joint both inducing a direct compressive force on the joint or leading to increased tension on ligamentous structures [Snijders CJ, 1993a,b; Vleeming A, 1990]. Coccygeus muscle – which crosses the sacroiliac joint – can determine a compressive force on the pelvis [Snijders CJ, 1993a,b]. Furthermore, motor control of the pelvic floor muscles [O'Sullivan P, 2002] and voiding dysfunction [O'Sullivan P, 2002; Pool-Goudzwaard AL, 2003] have been previously shown to be present in a group of patients diagnosed with sacroiliac joint pain. In addition, an association between urinary incontinence and arthritis was documented in an epidemiological study involving more than 25

thousand men [Finkelstein MM, 2001]. When in-vitro evaluations were conducted to test stress on bony structures – mimicking a pelvic floor muscles hypertonicity – an increase of sacroiliac joint stiffness was demonstrated [Pool-Goudzwaard AL, 2004]. A similar pathogenic mechanism might be responsible for the morphological modification of the coccygeal curvature in our study population. As previously described, a sustained hypertonic contraction of the pelvic floor muscles may pull the coccyx ventrally. This hypothesis seems to be coherent with previous publication in which a modified coccygeal angle was found in subjects with idiopathic coccygodynia [Kim NH, 1999; Maigne JY, 1996].

Based on the evidences produced with our research, we propose the following pathogenic mechanisms as underlying causes for PBNO:

- at a static evaluation, a horizontalization of the sacrum linked to an anteversion of the pelvis causes a flexion of the coccyx;
- when a dynamic approach is applied, postural imbalances identified at gait analysis determine an anomalous activation of the pelvic floor muscles, with consequent perineal plane hypertonicity;
- from a morphological and functional point of view, this is accompanied by a shortening of pelvic floor muscles length.

All these mechanisms may lead to urinary sphincters hypercontraction and to the development of urinary voiding symptoms in male patients with no significant morphological alterations. Moreover, a diffuse hypertonia of the pelvic floor may lead to a further modification of the coccygeal curvature, which consequently appears dysmorphic at X-ray and at magnetic resonance imaging.

In this setting, PBNO may be a possible presentation of the so called “overactive pelvic floor muscles” condition. This entity has been defined by the ICS as “a situation in which the pelvic floor muscles do not relax, or may even contract when relaxation is functionally needed for example during micturition or defecation” [Messelink B, 2005]. Consistently, all the patients who underwent neurophysiological evaluations in our research were confirmed to have muscular hypertonicity at electromyographic studies.

This proposed mechanism may also explain the evidence, in our study population, of erectile function impairment in up to 25% patients (n. 18/71), and of ejaculation disorders in 35% patients (n. 25/71). Pelvic floor hypertonicity due to postural imbalance may be the trigger for the development of symptoms during or immediately after erection and/or during ejaculation. An increased contraction (strengthening) of the urethral sphincters may sustain both a temporary reduction of blood flow at the perineum or distal urethra and a further compression on sensorial fibres directed to the perineum (pudendal nerves). The latter condition appears to be the most probable, as it can impact on the afferent way and contribute to an altered conduction of sensory information. In fact, several patients reported perineal pain or cramp, urethral discomfort or tingling sensation at the tip of the penis. The presence of a reduced ejaculated volume may depend on the incomplete relaxation of the external urethral sphincter, which is essential for a proper ejaculation. In the end, premature ejaculation was reported in some cases, but was considered not necessarily significant due to other possible variables as, for example, psychological aspects. Therefore, in the present research we decided not to evaluate the existence of an eventual correlation for this specific condition.

# IV. CONCLUSIONS

Male voiding dysfunction represents a challenging field for an open-minded Urologist. In fact, the physiological process of micturition may be affected by different factors as for example benign prostatic obstruction, cicatricial urethral strictures, diabetes, neurological diseases, cognitive impairment, constipation, drug effects, psychological aspects, alteration in metabolism and long-term effects of cigarette smoking. In this scenario, functional disorders of the urinary tract are frequently misunderstood or confused with other conditions. Due to the underestimation of the extent of pathology, patients bothered by urological functional disorders have been little investigated in the past. Among all the possible urological dysfunction, PBNO is one of the most frequent in males; in previous publications, it was diagnosed in up to 47-54% of male patients aged 18-45 years with chronic voiding symptoms. Therefore, a better understanding of the nature and aetiology of this disease is required. Understanding the cause/effect sequence may contribute to the identification of a better therapeutic workflow which necessarily requires multidisciplinary competences to be managed. Sometimes, changing perspective on a topic may add incredible information for a better comprehension. Therefore, we designed the present research with the innovative introduction of diagnostic procedures and evaluations typically not applied to urological patients.

In our research we proved that – when examining male patients with chronic voiding symptoms (with or without associated pelvic pain) suspected for PBNO – a comprehensive urologic, neurologic and pain assessment evaluations with deep pelvic floor muscle examination are required. This is crucial for the clear comprehension of patients' discomfort (for example, to rule out other possible interference factors), for the definition of the optimal diagnostic workflow, and for the identification of the best therapeutic approach.

The observations provided in this research are coherent with our initial hypothesis [Camerota TC, 2016]. Posture may have a direct impact and effect on micturition in males with no additional causes for voiding dysfunction, and therefore PBNO and postural imbalances may be two faces of the same coin. Our results are also consonant with other study populations' findings which showed an impact of posture on pelvic functions both during static [Capson AC, 2011; Halski T, 2014; Butrick CW, 2009b] or dynamic activities [Sapsford RR, 2001]; another research suggested the importance of pelvic floor spasm in the origin of voiding dysfunction (in females) [Kuo T, 2015].

The results obtained with our research on 71 male subjects diagnosed with PBNO may be summarized as follows:

- a variable combination of irritative and obstructive voiding symptoms are reported at the first clinical evaluation;
- pathologic flow characteristics were always present at uroflowmetry, with recurrent patterns (e.g.: plateau and stream intermittency);

- internal and external urethral sphincters hypercontraction (urethral functional stricture) was always found at a flexible outpatient urethrocystoscopy;
- myofascial pain syndrome was frequently diagnosed at pelvic pain assessment;
- hooked coccyx, lumbar hyperlordosis, short leg syndrome, and different degrees of modifications in spino-pelvic parameters (e.g.: pelvic tilt) were identified at full spine X-ray;
- external urethral sphincter thickening, pelvic floor muscles hypertonicity, hooked coccyx, sacroiliac joint sclerosis, and different degrees of modifications in spino-pelvic parameters (e.g.: pelvic tilt) were shown at MRI;
- different degrees of pudendal or sacral neuropathy were found at neurophysiological testing, while sustained contractions and/or poor post-contraction relaxations were found at EMG;
- non-subjectively perceived postural defects were identified in all the subjects who underwent gait analysis.

Uroflowmetry with PVR was confirmed to be – together with deep anamnestic investigation and bladder diary – an essential tool to suspect PBNO. Not only the procedure is diagnostic, but it can also be adopted in the follow-up schedule to monitor PVR and voided volumes, which appear to be significantly impacted in patients diagnosed with functional voiding dysfunction.

In a general framework, our data confirm that static and dynamic pelvic balances are associated with pelvic floor muscles hypertonicity which is in the end responsible for voiding symptoms. In our cohort of patients, voiding dysfunction and pain appear to derive

from a common pathogenetic mechanism: muscular hypertonicity is both a trigger for pain and an obstacle to normal urine flow. Moreover, these conditions contribute to an increase in intra-abdominal pressure which reasonably influence the increased frequency of abdominal hernias observed in our study population.

The evidence of both sacroiliac joint suffering and modifications in coccygeal appearance at imaging confirm the presence of an important hypertonic contraction of the pelvic floor muscles in patients diagnosed with PBNO. This hypertonicity is strictly associated with postural imbalances, as shown by kinematics. Gait analysis is a useful tool to quantitatively measure kinematic variables of human movement. In our research, this methodology showed a significant deviation from normalcy in PBNO patients, with alterations mainly at the pelvis and ankle levels. Unfortunately, it was not possible to identify a clear correlation between the severity of urological reported symptomatology and the altered gait pattern per each patient (as quantified by the gait score), maybe due to the reduced sample size. In addition, it was not possible to find a unique morphologic pattern at imaging.

Gait analysis is a reliable and reproducible functional test, it is both non-invasive and inexpensive. Unfortunately, gait evaluations are time-consuming and cannot be used on a routine basis due to equipment availability. Moreover, data analysis requires highly-specialized competences (e.g.: biomedical engineering). Furthermore, gait analysis is not currently recognized as a diagnostic procedure in Urology, and there is no reimbursement from the National Health System. Considering its positive characteristics, we propose gait

analysis as a potential innovative tool for longitudinal study and for monitoring clinical response to treatment in PBNO. To the best of our knowledge, this research is the first to investigate and to prove a correlation among voiding dysfunction and postural/kinematic patterns in males.

It was previously proposed that posture and locomotion might be influenced by pelvic floor muscles activity [Pool-Goudzwaard AL, 2004]. To date, it is still not completely defined if the pelvic floor controls movement of the sacrum (e.g.: nutation) or whether an imbalance of the pelvis determines hypercontraction of the pelvic floor muscles. Which came first: the egg or the chicken? The dilemma seems to be still unresolved. As shown with the neurophysiologic tests performed in this research, pelvic floor muscle hypertonicity may be associated to sympathetic hyperactivity, which might lead to tetanic contractions of the urethral sphincters. Pelvic floor hyperactivation has been proposed to be a form of compensation for decreased pelvic stability in females (e.g.: after pregnancy); but other explanations should be identified for males.

Pelvic floor hypertonicity is easy to be diagnosed and treated. In our opinion, the actual major limitation in the everyday clinical practice is represented by the fact that this condition is not looked for in males, and thus remains misunderstood. With our research we provide evidences proving that PBNO and pelvic floor muscles hypertonicity are strictly linked. Performing unconventional imaging in patients with dysfunctional voiding may be crucial to get an accurate diagnosis, thus leading to optimal clinical and therapeutic management. Therefore, multimodal comprehensive therapeutic

plans are essential to properly treat patients diagnosed with PBNO. Pelvic floor rehabilitation is a crucial component of this approach. Patients should first of all understand the normal function of their pelvic floor; relaxation exercises and physical manipulations represent a second step.

Our data support the evidence that integrated methods might provide more in-depth comprehension on the possible pathogenetic mechanisms and/or associated clinical conditions in PBNO. In fact, other than the association with pain – which was already previously described – we observed interesting correlations with postural defects, increased tone in pelvic floor muscles, skeletal disorders unknown by the patient, and inguinal hernias. Urethral sphincters hypertonicity, abdominal hernias, myofascial pain syndrome or articular pain may be seen as a unique set of medical signs and symptoms. Therefore, we propose this association as a possible new urological syndrome. Heartburn might be another symptom sustained by increased intra-abdominal pressures; unfortunately, sufficient data were not collected during this research. For these reasons we strongly recommend that a multidisciplinary approach involving wide-spectrum competencies in a tertiary-level Centre is adopted to adequately evaluate patients, and to provide them with the best possible opportunity (both diagnostic and therapeutic).

Post-treatment urological and clinical improvements were proved in the group of PBNO patients whose data were available. Improvements were both clinically perceived by patients (e.g.: reduction of myofascial pain and urinary frequency) and objectively identified (e.g.: better uroflowmetric parameters, normalization of

urinary frequency and voided volume at bladder diaries). PBNO and pelvic floor muscles hypertonicity are chronic disorders. Thus, post-treatment urological assessment should be carried out months after the beginning of rehabilitative treatments. The most suitable timing is debatable. Patients diagnosed with PBNO are extremely heterogeneous, therefore a unique scheme may not be indicated. It seems reasonable that the post-treatment schedule should be defined depending on the degree of the perceived discomfort by each single patient and on the severity of the initial urological disorder. Usually urological re-assessment is carried out with uroflowmetry and PVR, bladder diaries and clinical evaluation; invasive procedures should be avoided unless in case significant symptoms persist or in case non-invasive procedures are doubtful.

We strongly believe that our research may open up new possible horizons in the field of Urology. In fact, voiding symptoms and urological diseases were traditionally considered to be mostly surgical. Our recent innovative experience sustains the hypothesis that – if properly identified and diagnosed – there is a group of urological patients who may benefit from alternative treatments. Moreover, it is still well known that comprehensive treatments are more effective when the underlying mechanisms of a disease are properly understood. Therefore, results provided with our research appear to be relevant as they reveal an important need for rehabilitative medicine. This is even more meaningful if we look at the efforts that the Italian Legislator – both national and regional – is putting in place. Aging population generates new social and health needs for chronic patients. Thus, since a couple of years, in Lombardy region a process of progressive shift from the provision of

acute health services to the supply of comprehensive supports has been started. In this setting, patients are considered increasingly important; the proper identification of their real clinical needs will make it possible for the new system to properly work. Numerous scientific publications focused on the needs of specific patient subpopulations (e.g.: cancer patients, specific age groups, etc.), but very few focused on the needs of patients affected by chronic benign urological diseases. It is crucial to differentiate a “need” from the concept of “quality of life”; although they are strictly linked together, they are not really equivalent. In fact, a need may be defined as the requirement of a resource or a supply which is considered useful or necessary for a specific patient. Moreover, it is important to stress the relationship between needs and unmet needs. As a matter of fact, subjects affected by chronic dysfunctions are frequently not aware of their conditions, thus they do not perceive the opportunity to improve their personal health condition.

As in other fields of rehabilitative medicine, to date there is still insufficient knowledge of the real need for rehabilitation in Urology. Moreover, this demand should be considered in two different perspectives: 1. the number of newly diagnosed patients per year requiring for this health services; 2. the duration of treatments over time per single patient. Are these *una tantum* therapies or periodic treatments are needed? Differences may be identified if a stratification of study populations is done. Recent rehabilitative experiences in cancer patients showed a greater adherence to therapies in young patients [Susser RS, 2008], mainly females [Bjoernshave B, 2011], and/or with a higher socioeconomic status [Clark AM, 2012].

Based on the known epidemiological data, clinical experience and results provided by our research, Rehabilitative Urology behaves as an unmet need which may be defined as “a need that is not addressed or where additional support is required” [Vilstrup Holm, 2013]. In our opinion, the proper identification and characterization of these new needs – deriving from our changing society – represents the most ambitious challenge for innovative urologic services. Previous publications demonstrated that higher levels of psychological distress and poorer quality of life are mostly associated with unmet needs, at least in cancer patients [Vilstrup Holm, 2013]. As far as functional urology is a new developing discipline and diseases characterization is an ongoing process, epidemiological data are missing. Therefore, there is an actual lack of knowledge on rehabilitative requirements, and further researches are needed to define future directions.

Future researches are needed to verify after treatment results in the entire study population. Long-term follow-up (maintenance of clinical benefits over time) is also required. Cost/effect ratio needs to be thoroughly investigated. Moreover, additional research in the field of gait analysis applied to functional urological patients should be done. Further researches are also needed to better assess the cause/effect sequence between pelvic floor muscles hypertonicity and skeletal disorders (e.g.: hooked coccyx, sacroiliac joint dysfunction).

Although it has been described also in female patients, PBNO appears to be predominant in the male population. Epidemiology, clinical presentations and characteristics of symptoms are for many aspects similar to that of interstitial cystitis/bladder pain syndrome,

more typical in the female population. Previous publications demonstrated an increase in urethral pressures in females diagnosed with interstitial cystitis/bladder pain syndrome when compared to normal subjects [Butrick CW, 2009a; Cameron AP, 2009]. In our opinion, this evidence may depend on a hypertonic pelvic floor, coherently to what we hypothesised in this doctoral research for PBNO. Therefore, we propose that interstitial cystitis may represent the female counterpart of the male patients PBNO. To the best of our knowledge, nobody has comparatively studied and compared these two diseases, nor has proposed a possible common aetiology. For these reasons we think it could be of interest to reproduce our research methodologies also in patients with interstitial cystitis/bladder pain syndrome. If the proposed diagnostic work-up (magnetic resonance imaging, spine X-ray and gait analysis) will be verified, it may open new insights, eventually showing a common etiopathogenesis for both the diseases. A better comprehension of the underlying pathogenic mechanisms will allow the identification of more adequate therapeutic schemes; in fact, it is not infrequent for these patients to move from urologist to urologist in the hope to receive more effective therapies, as already described for PBNO.

# REFERENCES


Abrams P et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21(2):167-78.

Abrams P et al. Standardisation sub-committee of the International Continence Society. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology. 2003;61:37–49.

Abrams P et al. Reviewing the ICS 2002 terminology report: The ongoing debate. Neurourol Urodyn. 2006;25(3):293.

Abrams P et al. Incontinence. 5th International Consultation on Incontinence. 5th Edition, ICUD-EAU 2013.

Ackerman AL, Rodriguez LV. Evaluation of Primary Bladder Neck Obstruction in Men. Curr Bladder Dysfunct Rep (2012) 7:235–241.

Adrián-Arrieta L, Casas-Fernández de Tejerina JM. Self-perception of disease in patients with chronic diseases. Semergen. 2017 Nov 18. pii: S1138-3593(17)30283-6.

Altomare DF, Rinaldi M, Veglia A, Guglielmi A, Sallustio PL, Tripoli G. Contribution of posture to the maintenance of anal continence. Int J Colorectal Dis. 2001 Feb;16(1):51-4.

Amonoo-Kuofi HS. Changes in the lumbosacral angle, sacral inclination and the curvature of the lumbar spine during aging. Acta Anat 1992;145:373–7.

Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. Ann N Y Acad Sci 2007;1101:266-96.

Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. Neurourol Urodyn. 2004;23(4):322-30.

Awad SA, Downie JW, Lywood DW, Young RA, Jarzylo SV. Sympathetic activity in the proximal urethra in patients with urinary obstruction. J Urol. 1976;115:545–7.

Axelrod SL, Blaivas JG. Bladder neck obstruction in women. J Urol. 1987;137:497–499.

Ayoub SF. The anterior fibres of the levator ani muscle in man. J Anat. 1979 May;128(Pt 3):571-80.

Barrey C, Roussouly P, Le Huec JC, D'Acunzi G, Perrin G. Compensatory mechanisms contributing to keep the sagittal balance of the spine. Eur Spine J. 2013 Nov;22 Suppl 6:S834-41.

Barry MJ, Fowler FJ, O'leary MP et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. Journal of Urology 1992;148:1549-1557.

Bayne DB, Gaither TW, Awad MA, Murphy GP, et al. Guidelines of guidelines: a review of urethral stricture evaluation, management, and follow-up. Transl Androl Urol. 2017 Apr;6(2):288-294.

Bharucha AE, Fletcher JG, et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence. Gut 2005;54:546–555.

Bharucha AE, Fletcher JG, et al. Recent advances in assessing anorectal structure and functions. Gastroenterology 2007;133:1069–1074

Bjoernshave B, Korsgaard J, Jensen C, Nielsen CV. Participation in pulmonary rehabilitation in routine clinical practice. Clin Respir J. 2011 Oct;5(4):235-44.

Bø K, Sherburn M. Evaluation of female pelvic-floor muscle function and strength. Phys Ther. 2005 Mar;85(3):269-82.

Bortolotti A, Bernardini B, Colli E, Dibendetto P, Nacci GG, Landoni M et al. Prevalence and risk factors for urinary incontinence in Italy. Eur Urol, 2000;37:30.

Bosch J, Abrams P, Cotterill N, et al. Etiology, patient assessment and predicting outcome from therapy. In: Chapple C, Abrams P, editors. Male lower urinary tract symptoms. Montreal, Canada: International Consultation on Urological Diseases Male LUTS Guideline; 2013. p. 37–133.

Boyle P, Boyle P, Robertson C, Mazzetta C, Keech M, Hobbs FD, Fourcade R, et al. The UrEpik Study Group. The prevalence of male urinary incontinence in four centres: the UREPIK study. BJU Int., 92:943, 2003.

Broadhurst NA, Bond MJ. Pain provocation tests for the assessment of sacroiliac joint dysfunction. J Spinal Disord. 1998 Aug;11(4):341-5

Brooks JD, Chao WM, Kerr J. Male pelvic anatomy reconstructed from the visible human data set. J Urol. 1998 Mar;159(3):868-72.

Burkhard FE, Lucas MG, Berghmans LC, Bosch JLHR, et al. EAU 2016 Guidelines on Urinary Incontinence in Aduts. Available at https://uroweb.org/wp-content/uploads/EAU-Guidelines-Urinary-Incontinence-2016.pdf (last consultation on December 09th, 2017).

Burnett AL, Mostwin JL. In situ anatomical study of the male urethral sphincteric complex: relevance to continence preservation following major pelvic surgery. J Urol. 1998 Oct;160(4):1301-6.

Butrick CW, Sanford D, Hou Q, Mahnken JD. Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations. Int Urogynecol J Pelvic Floor Dysfunct. 2009a Sep;20(9):1047-53.

Butrick CW. Pathophysiology of pelvic floor hypertonic disorders. Obstet Gynecol Clin N Am 2009b;36:699-705.

Butrick CW. Pelvic floor hypertonic disorders: identification and management. Obstet Gynecol Clin N Am 2009c;36:707-722.

Cameron AP, Gajewski JB. Bladder outlet obstruction in painful bladder syndrome/interstitial cystitis. Neurourol Urodyn. 2009;28(8):944-8.

Camerota TC, Zago M, Pisu S, Ciprandi D, Sforza C. Primary bladder neck obstruction may be determined by postural imbalances. Med Hypotheses. 2016 Dec;97:114-116.

Capson AC, Nashed J, Mclean L. The role of lumbopelvic posture in pelvic floor muscle activation in continent women. J Electromyogr Kinesiol. 2011 Feb;21(1):166-77.

Chan SSC, et al. Responsiveness of the Pelvic Floor Distress Inventory and Pelvic Floor Impact Questionnaire in women undergoing treatment for pelvic floor disorders. Int Urogynecol J, 2013. 24: 213.

Chen JL, Chen CY, Kuo HC. Botulinum toxin A injection to the bladder neck and urethra for medically refractory lower urinary tract symptoms in men without prostatic obstruction. J Formos Med Assoc. 2009 Dec;108(12):950-6.

Cholewicki J, Juluru K, McGill SM. Intra-abdominal pressure mechanism for stabilizing the lumbar spine. J Biomech. 1999a Jan;32(1):13-7.

Cholewicki J, Juluru K, Radebold A, Panjabi MM, McGill SM. Lumbar spine stability can be augmented with an abdominal belt and/or increased intra-abdominal pressure. Eur Spine J. 1999;8(5):388-95.

Cimolin V, Galli M. Summary measures for clinical gait analysis: a literature review. Gait Posture. 2014 Apr;39(4):1005-10.

Clark AM, et al. A qualitative systematic review of influences on attendance at cardiac rehabilitation programs after referral. Am Heart J. 2012 Dec;164(6):835-45.

Coyne K, Kelleher C. Patient reported outcomes: the ICIQ and the state of the art. Neurourol Urodyn. 2010 Apr;29(4):645-51.

Dansie EJ, Turk DC. Assessment of patients with chronic pain. Br J Anaesth. 2013 Jul;111(1):19-25.

de Groat WC, et al. Spinal cord projections and neuropeptides in visceral afferent neurons. Prog Brain Res. 1986; 67:165–187.

de Groat WC, et al. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Prog Brain Res. 2006; 152:59–84.

de Groat WC, et al. Neural control of the lower urinary tract. Compr Physiol. 2015 Jan;5(1):327-96.

DeLong J, Buckley J. Patient-reported outcomes combined with objective data to evaluate outcomes after urethral reconstruction. Urology. 2013;81:432–436.

Deluzio KJ, Wyss UP, Costigan PSA, Sorbie C, Zee B. Gait assessment in unicompartimental knee arthroplasty patients: principal component modelling of gait waveforms and clinical status. Human Movement Science. 1999. 18(5):701-711.

Digesu GA, et al. Three-dimensional ultrasound of the urethral sphincter predicts continence surgery outcome. Neurourol Urodyn, 2009. 28: 90.

Diokno AC, et al. Bladder neck obstruction in women: a real entity. J Urol. 1984;132:294–298.

Diokno AC, et al. Prevalence of urinary incontinence in community dwelling men: a cross sectional nationwide epidemiology survey. Int Urol Nephrol 39:129-36, 2007.

During J, Goudfrooij H, Keessen W, Beeker TW, Crowe A. Towards standards for posture. Postural characteristics of the lower back system in normal and pathologic conditions. Spine. 1985;10:83–87.

Eisenstein SM, Engelbrecht DJ, el Masry WS. Low back pain and urinary incontinence. A hypothetical relationship. Spine (Phila Pa 1976). 1994 May 15;19(10):1148-52.

Engstrom G, Walker-Engstrom ML, Loof L, Leppert J. Prevalence of three lower urinary tract symptoms in men - a population-based study. Fam Pract, 2003;20:7.

Espuña-Pons M, Brugulat Guiteras P, Costa Sampere D, Medina Bustos A, Mompar. Prevalence of urinary incontinence in Catalonia, Spain. Penina A. Med Clin (Barc). 2009 Nov 14;133(18):702-5.

Essendrop M, Trojel Hye-Knudsen C, Skotte J, Faber Hansen A, Schibye B. Fast development of high intra-abdominal pressure when a trained participant is exposed to heavy, sudden trunk loads. Spine (Phila Pa 1976). 2004 Jan 1;29(1):94-9.

Finkelstein MM. Medical conditions, medications and urinary incontinence. Analysis of a population-based survey. Can Fam Physician 2001;48:96-101.

Fletcher JG, Busse RF, Riederer SJ, et al. Magnetic resonance imaging of anatomic and dynamic defects of the pelvic floor in defecatory disorders. Am J Gastroenterol 2003;98:399–411.

Fowler CJ, Griffiths D, de Groat WC. Integrated control of lower urinary tract-clinical perspective. Br J Pharmacol 2006;147:S14-24.

Fowler CJ, Griffiths D, de Groat WC. The neural control of micturition. Nat Rev Neurosci. 2008 Jun;9(6):453-66.

Glassberg KI, Combs AJ, Horowitz M. Nonneurogenic voiding disorders in children and adolescents: clinical and videourodynamic findings in 4 specific conditions. J Urol. 2010;184:2123–7.

Goldman HB, Zimmern PE. The treatment of female bladder outlet obstruction. B J Urol Int 2006, 98(suppl 1):17-23.

Gosling JA and Dixon JS. The structure and innervation of smooth muscle in the wall of the bladder neck and proximal urethra. Br J Urol, 1975. 47(5): p. 549-58.

Gosling JA and Dixon JS. Functional anatomy of the urinary tract: an integrated text and colour atlas. Edinburgh: Churchill Livingstone, 1983, c1982.

Grafstein NH, Combs AJ, Glassberg KI. Primary bladder neck dysfunction: an overlooked entity in children. Curr Urol Rep. 2005;6:133–9.

Gratzke C, Bachmann A, Descazeaud A, Drake MJ, et al. EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction. Eur Urol. 2015 Jun;67(6):1099-1109.

Haanpää M, Attal N, Backonja M et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011 Jan;152(1):14-27.

Hadley HR, Zimmermann PE, Raz S. The treatment of male urinary incontinence. Campbell's Urology, M.F. Campbell and P.C. Walsh, Editors. 1986, Saunders: London. p. 2297-3039.

Hague M, Shenker N. How to investigate: Chronic pain. Best Pract Res Clin Rheumatol. 2014 Dec;28(6):860-74.

Halski T, Słupska L, Dymarek R, Bartnicki J, Halska U, et al. Evaluation of bioelectrical activity of pelvic floor muscles and synergistic muscles depending on orientation of pelvis in menopausal women with symptoms of stress urinary incontinence: a preliminary observational study. Biomed Res Int. 2014;2014:274938.

Herschorn A, Gajewski J, Schulz J, and Corcos J. A population-based study of urinary symptoms and incontinence: the Canadian urinary bladder survey. BJU Int, 2007;101: 52-8.

Hetrick DC, Ciol MA, Rothman I, Turner JA, Frest M, Berger RE. Musculoskeletal dysfunction in men with chronic pelvic pain syndrome type III: a case-control study. J Urol. 2003 Sep;170(3):828-31.

Hodges PW, Butler JE., McKenzie, D.K., Gandevia, S.C., 1997. Contraction of the human diaphragm during rapid postural adjustments. J Physiol. 1997 Dec 1;505 (Pt 2):539-48.

Hollabaugh RS Jr et al. Preservation of putative continence nerves during radical retropubic prostatectomy leads to more rapid return of urinary continence. Urology, 1998. 51(6): p. 960-7.

Hoyte L, Jakab M, Warfield SK, Shott S, Flesh G, Fielding JR. Levator ani thickness variations in symptomatic and asymptomatic women using magnetic resonance-based 3-dimensional color mapping. Am J Obstet Gynecol. 2004 Sep;191(3):856-61.

Hungerford B, Gilleard W, Lee D. Altered patterns of pelvic bone motion determined in subjects with posterior pelvic pain using skin markers. Clin Biomech (Bristol, Avon). 2004 Jun;19(5):456-64.

Irani J, Brown CT, van der Meulen J, Emberton M. A review of guidelines on benign prostatic hyperplasia and lower urinary tract symptoms: are all guidelines the same? BJU Int 2003;92:937–42.

Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, et al. Population-based survey of urinary incontinence, overactive bladder and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol, 2006;50(6):1306-15.

Jackson RP, Kanemura T, Kawakami N, Hales C. Lumbopelvic lordosis and pelvic balance on repeated standing lateral radiographs of adult volunteers and untreated patients with constant low back pain. Spine. 2000;25:575–586.

Jänig W, Morrison JFB. Functional properties of spinal visceral afferents supplying abdominal and pelvic organs, with special emphasis on visceral nociception. Prog Brain Res. 1986; 67:87–114.

Jorgensen JB, Jensen KM, Mogensen P. Age-related variation in urinary flow variables and flow curve patterns in elderly males. Br J Urol 1992;69:265–71.

Kaplan SA, et al. Urodynamic evidence of vesical neck obstruction in men with misdiagnosed chronic nonbacterial prostatitis and the therapeutic role of endoscopic incision of the bladder neck. J Urol. 1994;152:2063–5.

Kaplan SA, et al. Etiology of voiding dysfunction in men less than 50 years of age. Urology 1996;47:836–9.

Karam I et al. The structure and innervation of the male urethra: histological and immunohistochemical studies with three-dimensional reconstruction. J Anat, 2005. 206(4): p. 395-403.

Kessler TM, Studer UE, Burkhard FC. The effect of terazosin on functional bladder outlet obstruction in women: a pilot study. J Urol. 2006 Oct;176(4 Pt 1):1487-92.

Kim J, et al. Is there a relationship between incontinence impact questionnaire 7 score after surgery for stress urinary incontinence and patient-perceived satisfaction and improvement? 2013. Neurourol Urodyn 189:4 SUPPL. e647.

Kim NH, Suk KS. Clinical and radiological differences between traumatic and idiopathic coccygodynia. Yonsei Med J. 1999 Jun;40(3):215-20.

Kisner C, Colby LA. Therapeutic exercise: Foundations and techniques (6th ed., 1996). Philadelphia: F.A. Davis.

Kluck P. The autonomic innervation of the human urinary ladder, bladder neck and urethra: a histochemical study. Anat Rec, 1980;198:439-447.

Koskimaki J, Hakama M, Huhtala H and Tammela TL. Association of non-urological diseases with lower urinary tract symptoms. Scand J Urol Nephrol. 2001 Oct;35(5):377-81.

Kranse R, van Mastrigt R. Causes for variability in repeated pressure-flow measurements. Urology 2003;61:930–4.

Kuo TL, Ng LG, Chapple CR. Pelvic floor spasm as a cause of voiding dysfunction. Curr Opin Urol. 2015 Jul;25(4):311-6.

Kupelian V, Wei JT, O'Leary MP, et al. Prevalence of lower urinary tract symptoms and effect on quality of life in a racially and ethnically diverse random sample: the Boston Area Community Health (BACH) Survey. Arch Intern Med 2006;166:2381–7.

Leadbetter GW, Leadbetter WF. Diagnosis and treatment of congenital bladder neck obstruction in children. N Engl J Med. 1959;260:633.

Light HG, Routledge JA. Intra-abdominal pressure factor in hernia disease. Arch Surg. 1965 Jan;90:115-7.

Lockhart ME, et al. Reproducibility of dynamic MR imaging pelvic measurements: a multiinstitutional study. Radiology, 2008. 249: 534.

Lucas MG, Bosch RJL, Burkhard FC, Cruz F, Madden TB, et al. EAU guidelines on surgical treatment of urinary incontinence. Eur Urol. 2012;62:1118–29.

Luschka H. U¨ ber den vorderen inneren Teil des Afterhebers beim Manne. Zeitschrift fu¨r rationelle Medizin Serie 3 1858; 4: 108–16.

Maigne JY, Tamalet B. Standardized radiologic protocol for the study of common coccygodynia and characteristics of the lesions observed in the sitting position. Clinical elements differentiating luxation, hypermobility, and normal mobility. Spine (Phila Pa 1976). 1996 Nov 15;21(22):2588-93.

Malmsten UG, Milsom I, Molander U, and Norlen LJ. Urinary incontinence and lower urinary tract symptoms: an epidemiological study of men aged 45-99 years. J Urol., 158:1733, 1997.

Maral I, Ozkardes H, Peskircioglu L, and Bumin MA. Prevalence of stress urinary incontinence in both sexes at or after age 15 years: a cross-sectional study. J Urol., 165:408, 2001.

Marion G. Surgery of the neck of the bladder. Br J Urol 1933, 5:351–357.

Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. World J Urol 2011;29:179–84.

Mayer RD, Howard FM. Sacral nerve stimulation: neuromodulation for voiding dysfunction and pain. Neurotherapeutics. 2008 Jan;5(1):107-13.

McGrother CW, Donaldson MMK, Shaw C, Matthews RJ, Hayward TA, et al. Storage symptoms of the bladder: prevalence, incidence and need for services in the UK. BJU Int 93:763-69, 2004.

McVary KT, et al. Lower urinary tract symptoms and sexual dysfunction: epidemiology and pathophysiology. BJU Int 2006;97(Suppl 2):23-8.

McVary KT, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol 2011;185:1793–803.

Messelink B, et al. Standardization of terminology of pelvic floor muscle function and dysfunction: report from the pelvic floor clinical assessment group of the International Continence Society. Neurourol Urodyn. 2005;24(4):374-80.

Mishra VK, Kumar A, Kapoor R, Srivastava A, Bhandari M. Functional bladder neck obstruction in males: a progressive disorder? Eur Urol. 1992;22:123–9.

Morey AF, McAninch JW, Duckett CP, Rogers RS. American Urological Association symptom index in the assessment of urethroplasty outcomes. J Urol. 1998;159:1192–1194.

Morgan DM, et al. Urethral sphincter morphology and function with and without stress incontinence. J Urol, 2009. 182: 203.

Morrison JF, Birder L, Craggs M. Neural control. In: Abrams, P.; Cardozo, L.; Khoury, S.; Wein, A., editors. Incontinence. Plymouth, UK: Health Publication Ltd; 2005. p. 363-422.

Mullis C, Bavendam T, Kirkali Z, Kusek JW. Novel research approaches for interstitial cystitis/bladder pain syndrome: thinking beyond the bladder. Transl Androl Urol 2015;4(5):524-533.

Myers RP, Cahill DR, Kay PA, Camp JJ, Devine RM, King BF, Engen DE. Puboperineales: muscular boundaries of the male urogenital hiatus in 3D from magnetic resonance imaging. J Urol. 2000 Oct;164(4):1412-5.

Narouze SN. Atlas of Ultrasound-Guided Procedures in Interventional Pain Management. Springer-Verlag New York, 2011.

National Institute for Health and Clinical Excellence. The management of lower urinary tract symptoms in men. (Clinical Guideline 97.) 2010. http://guidance.nice.org.uk/CG97 (last consultation on December 10th, 2017).

Nguyen JK, Lind LR, Choe JY, McKindsey F, Sinow R, Bhatia NN. Lumbosacral spine and pelvic inlet changes associated with pelvic organ prolapse. Obstet Gynecol. 2000 Mar;95(3):332-6.

Nguyen L, et al. Surgical technique to overcome anatomical shortcoming: balancing postprostatectomy continence outcomes of urethral sphincter lengths on preoperative magnetic resonance imaging. J Urol, 2008. 179: 1907.

Nitti VW, et al. Diagnosing bladder outlet obstruction in women. J Urol. 1999;161:1535–1540.

Nitti VW, et al. Lower urinary tract symptoms in young men: videourodynamic findings and correlation with non-invasive measures. J Urol 2002;168:135–8.

Nitti VW, et al. Primary bladder neck obstruction in men and women. Rev Urol 2005;7:S12–7.

Norlen LJ, Blaivas JG. Unsuspected proximal urethral obstruction in young and middle-aged men. J Urol. 1986;135:972–6.

Novara G, Galfano A, Gardi M, Ficarra V, Boccon-Gibod L, Artibani W. Critical review of guidelines for BPH diagnosis and treatment strategy. Eur Urol Suppl 2006;4:418–29.

Nuss G Granieri MA, Zhao LC, Thum DJ, Gonzalez CM R. Presenting symptoms of anterior urethral stricture disease: a disease specific, patient reported questionnaire to measure outcomes. J Urol. 2012 Feb; 187(2):559-62.

O'Sullivan PB, Beales DJ, Beetham JA, Cripps J, Graf F, et al. Altered motor control strategies in subjects with sacroiliac joint pain during the active straight-leg-raise test. Spine (Phila Pa 1976). 2002 Jan 1;27(1):E1-8.

Padoa A, Rosenbaum TY. The overactive pelvic floor (1st Ed, 2016). Springer International Publishing. ISBN 978-3-319-22150-2

Pescatori M et al. Imaging atlas of the pelvic floor and anorectal diseases (1st Ed, 2008). Springer-Verlag Mailand. ISBN 978-88-470-0808-3

Peters KM. Neuromodulation for the treatment of refractory interstitial cystitis. Rev Urol. 2002;4 Suppl 1:S36-43.

Peters KM. Frequency, urgency, and pelvic pain: treating the pelvic floor versus the epithelium. Curr Urol Rep. 2006 Nov;7(6):450-5.

Pisu S. Analisi cinematica della deambulazione in soggetti affetti da disturbi urologici. Graduation thesis. School of Motor Sciences, University of Milan. Academic Year 2014-2015.

Pool-Goudzwaard AL. 2003. Biomechanics of the Sacroiliac Joints and the Pelvic Ring. Thesis, Erasmus University Rotterdam.

Pool-Goudzwaard AL, van Dijke GH, van Gurp M, Mulder P, Snijders C, Stoeckart R. Contribution of pelvic floor muscles to stiffness of the pelvic ring. Clin Biomech (Bristol, Avon). 2004 Jul;19(6):564-71.

Porzionato A, Macchi V, Gardi M, Parenti A, De Caro R. Histotopographic study of the rectourethralis muscle. Clin Anat. 2005 Oct;18(7):510-7.

Rocco F, Carmignani L, Acquati P, Gadda F, Dell'Orto P, et al. Early continence recovery after open radical prostatectomy with restoration of the posterior aspect of the rhabdosphincter. Eur Urol. 2007 Aug;52(2):376-83.

Rosen R, Altwein J, Boyle P, Kirby R, Lukacs B, Meuleman E, et al. Lower urinary tract symptoms and male sexual dysfunction: the Multinational Survey of the Aging Male (MSAM-7). Eur Urol 2003:44:637-49

Rosier PFWM, Schaefer W, Lose G, Goldman HB, et al. Urodynamic testing, Chapter 6. In Incontinence. Ed: Abrams P et al. 5th Edition. 2013. International Consultation on Urologic Disease. 5th International Consultation on Incontinence; Recommendations of the International Scientific Committee: Evaluation and Treatment of Urinary Incontinence, Pelvic Organ Prolapse and Faecal Incontinence. eds. Paris: ICUD-EAU 2013. 2013a.

Rosier PFWM. The evidence for urodynamic investigation of patients with symptoms of urinary incontinence. F1000Prime Rep;5:8. 2013b.

Rosier PFWM, et al. International Continence Society Good Urodynamic Practices and Terms 2016: Urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourol Urodyn. 2017 Jun;36(5):1243-1260.

Roussouly P, Gollogly S, Berthonnaud E, Dimnet J. Classification of the normal variation in the sagittal alignment of the human lumbar spine and pelvis in the standing position. Spine. 2005;30:346–353.

Sacco E, Tienforti D, Bientinesi R, D'Addessi A, Racioppi M, et al. OnabotulinumtoxinA injection therapy in men with LUTS due to primary bladder-neck dysfunction: objective and patient-reported outcomes. Neurourol Urodyn. 2014 Jan;33(1):142-6.

Sahinkanat T, Arıkan DC, Turgut E, Ozkurkcugil C, Yılmaz H, Ekerbicer H. Effects of lumbar lordosis and pelvic inlet orientation on the outcome of the transobturator tape sling operation in women. Arch Gynecol Obstet. 2011 Jul;284(1):125-30.

Salvati EP. The levator syndrome and its variant. Gastroenterol Clin North Am. 1987 Mar;16(1):71-8.

Sapsford RR, Hodges PW. Contraction of the pelvic floor muscles during abdominal maneuvers. Arch Phys Med Rehabil. 2001 Aug;82(8):1081-8.

Schlomm T, et al. Full functional-length urethral sphincter preservation during radical prostatectomy. Eur Urol, 2011.60(2):320-9.

Sebe P et al. Fetal development of striated and smooth muscle sphincters of the male urethra from a common primordium and modifications due to the development of the prostate: an anatomic and histologic study. Prostate, 2005a. 62(4): p. 388-93.

Sebe P et al. An embryological study of fetal development of the rectourethralis muscle--does it really exist? J Urol. 2005b Feb;173(2):583-6.

Segura JW, Opitz JL, Greene LF. Prostatosis, prostatitis or pelvic floor tension myalgia? J Urol. 1979 Aug;122(2):168-9.

Shamliyan TA, Wyman JF, Ping R, Wilt TJ, Kane RL. Male urinary incontinence prevalence, risk factors, and preventive interventions. Rev Urol 2009;11(3):145-65.

Shirley D, Hodges PW, Eriksson AE, Gandevia SC. Spinal stiffness changes throughout the respiratory cycle. J Appl Physiol (1985). 2003 Oct;95(4):1467-75.

Simon, SR. Quantification of human motion: gait analysis-benefits and limitations to its application to clinical problems. J Biomech. 2004 Dec;37(12):1869-80.

Siroky MB, Olsson CA, Krane RJ. The flow rate nomogram: II. Clinical correlation. J Urol 1980;123:208–10.

Smoger SH, Felice TL, and Kloecker GH. Urinary incontinence among male veterans receiving care in primary care clinics. Ann Intern Med., 132:547, 2000.

Snijders CJ, Vleeming A, Stoeckart R. Transfer of lumbosacral load to iliac bones and legs Part 1: Biomechanics of self-bracing of the sacroiliac joints and its significance for treatment and exercise. Clin Biomech (Bristol, Avon). 1993a Nov;8(6):285-94.

Snijders CJ, Vleeming A, Stoeckart R. Transfer of lumbosacral load to iliac bones and legs Part 2: Loading of the sacroiliac joints when lifting in a stooped posture. Clin Biomech (Bristol, Avon). 1993b Nov;8(6):295-301.

Speakman MJ, Kirby RS, Joyce A, Abrams P, Pocock R. Guideline for the primary care management of male lower urinary tract symptoms. BJU Int 2004;93:985-90.

Stav K, Alcalay M, Peleg S, Lindner A, Gayer G, Hershkovitz I. Pelvis architecture and urinary incontinence in women. Eur Urol. 2007 Jul;52(1):239-44.

Stoffel JT. Detrusor sphincter dyssynergia: a review of physiology, diagnosis, and treatment strategies. Transl Androl Urol. 2016 Feb;5(1):127-35.

Strasser H, Bartsch G. Anatomy and innervation of the rhabdosphincter of the male urethra. Semin Urol Oncol. 2000 Feb;18(1):2-8.

Susser RS, McCusker J, Belzile E. Comorbidity information in older patients at an emergency visit: self-report vs. administrative data had poor agreement but similar predictive validity. J Clin Epidemiol. 2008 May;61(5):511-5.

Tam CA, et al. The International Prostate Symptom Score (IPSS) Is an Inadequate Tool to Screen for Urethral Stricture Recurrence After Anterior Urethroplasty. Urology. 2016 Sep; 95: 197–201.

Toh KL, Ng CK. Urodynamic studies in the evaluation of young men presenting with lower urinary tract symptoms. Int J Urol. 2006;13:520–3.

Tran MGB, et al. Prospective assessment of patient reported outcome measurements (PROMs) in male stress incontinence (MSI) surgery. Neurourol Urodyn 2013. 11 59.

Trockman BA, et al. Primary bladder neck obstruction: urodynamic findings and treatment results in 36 men. J Urol. 1996;156:1418–20.

Tubaro A, Nambiar AK. Grey zone: urinary incontinence. Eur Urol Focus. 2016 Aug;2(3):337-338.

Turner-Warwick R, Whiteside C, Worth P, Milroy E, Bates C. A urodynamic view of the clinical problems associated with bladder neck dysfunction and its treatment by endoscopic incision and transtrigonal posterior prostatectomy. Br J Urol 1973;45:44–59.

Van Oyen H, Van Oyen P. Urinary incontinence in Belgium; prevalence, correlates and psychosocial consequences. Acta Clin Belg., 57:207, 2002.

Van Waalwijk van Doorn E, Anders K, Khullar V, et al. Standardisation of ambulatory urodynamic monitoring: report ofthe sandardisation sub-committee of the International ContinenceSociety for Ambulatory Urodynamic Studies. Neurourol Urodyn.2000;19:113–125.

Vaz G, Roussouly P, Berthonnaud E, Dimnet J. Sagittal morphology and equilibrium of pelvis and spine. Eur Spine J. 2002;11x:80–87.

Vilstrup Holm L. Danish cancer patients' rehabilitation needs, participation in rehabilitation activities and unmet needs. PhD thesis, 2013. University of Southern Denmark.

Vleeming A, Buyruk HM, Stoeckart R, Karamursel S, Snijders CJ. An integrated therapy for peripartum pelvic instability: a study of the biomechanical effects of pelvic belts. Am J Obstet Gynecol. 1992 Apr;166(4):1243-7.

Vuichoud C, Loughlin KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can J Urol. 2015 Oct;22 Suppl 1:1-6.

Wallner C et al. The anatomical components of urinary continence. Eur Urol, 2009. 55(4): p. 932-43.

Walters MD, Karram MM. Urogynecology and Reconstructive Pelvic Surgery, fourth edition. Elsevier Saunders, Philadelphia, 2014. ISBN: 9780323113779.

Waltz J, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol. 2010 Feb;57(2):179-92.

Webster GD, Lockhart JL, Older RA. The evaluation of bladder neck dysfunction. J Urol 1980;123:196-198.

Weiselfish Giammatteo S, Giammatteo T. Integrative manual therapy for biomechanics, application of muscle energy and beyond technique: treatment of the Spine, Ribs, and Extremities. Berkeley: North Atlantic Books; 2003. p. 225–8.

Weiss JM. Pelvic floor myofascial trigger points: manual therapy for interstitial cystitis and the urgency-frequency syndrome. J Urol. 2001 Dec;166(6):2226-31.

White G, Jantos M, Glazer H. Establishing the diagnosis of vulvar vestibulitis. J Reprod Med. 1997 Mar;42(3):157-60.

Woodfield CA, et al. Imaging pelvic floor disorders: trend toward comprehensive MRI. AJR Am J Roentgenol, 2010. 194: 1640.

Woodside JR. Urodynamic evaluation of dysfunctional bladder neck obstruction in men. J Urol. 1980;124:673–7.

Yang SS, Wang CC, Hsieh CH, Chen YT. Alpha1-Adrenergic blockers in young men with primary bladder neck obstruction. J Urol. 2002;168:571–4.

Yap TL, Cromwell DC, Emberton M. A systematic review of the reliability of frequency-volume charts in urological research and its implications for the optimum chart duration. BJU Int. 2007 Jan;99(1):9-16.

Yoshimura N, de Groat WC. Neural control of the lower urinary tract. Int J Urol. 1997; 4:111–125.

Zago M, Camerota TC, Pisu S, Ciprandi D, Sforza C. Gait analysis of young male patients diagnosed with primary bladder neck obstruction. J Electromyogr Kinesiol. 2017 Aug;35:69-75.

Zalewska E, Rowińska-Marcińska K, Hausmanowa-Petrusewicz I. Shape irregularity of motor unit potentials in some neuromuscular disorders. Muscle Nerve. 1998 Sep;21(9):1181-7.

Zhai LD, Liu J, Li YS, Ma QT, Yin P. The male rectourethralis and deep transverse perineal muscles and their relationship to adjacent structures examined with successive slices of celloidin-embedded pelvic viscera. Eur Urol. 2011 Mar;59(3):415-21.